Simple Boronic Acid Based NMR Protocols for Determining the Enantiomeric Excess of Chiral Amines, Hydroxylamines and Diols

Tickell, David

Award date:
2015

Awarding institution:
University of Bath

Simple Boronic Acid Based NMR Protocols for Determining the Enantiomeric Excess of Chiral Amines, Hydroxylamines and Diols

David Andrew Tickell

A thesis submitted for the degree of Doctor of Philosophy

University of Bath

Department of Chemistry

April 2015

COPYRIGHT

Signature ……. Date ...…..…….

"The Dark Lord was suddenly aware of him, and his Eye piercing all shadows looked across the plain to the door that he had made."

- J. R. R. Tolkien 1955

"I've seen things you people wouldn't believe.

Attack ships on fire off the shoulder of Orion.

I watched c-beams glitter in the dark near the Tannhäuser Gate.

All those moments will be lost in time, like tears in rain.

Time to die"

- Roy Batty 1982

"Honesty is my only excuse."

- James Hetfield 1986

"I'm digging my way to something better."

- James Hetfield 1997

Acknowledgements

Firstly, I would like to thank Dr. Steven Bull for giving me the push and drive to complete my PhD and for all his support over the last 7 years. My thanks go to Professor Tony James for offering me the chance to do a PhD and encouraging me to take the opportunities afforded to me. I'd like to thank all those who believed in me and took a chance on me when others, including myself, didn't believe. Who would have thought when I was failing my second year that I would be writing a thesis for my PhD 8 years later…

Thanks go to all the Bull and James group members who I have shared offices with over the last 4 and a half years, in particular Richard Blackburn, Robert Chapman, Emma Lampard and Ruth Lawrence for the entertainment, cups of tea and pieces of cake. To Jake for flying back from the deepest depths of Africa every few months to drink cider and enjoy the sights and sounds of Bath and to Jamie Belham, Topher Ecott and James Trebilco for being great friends and visiting me in Bath after they had all finished their degrees.

I'd like to thank Professor Kazuo Sakurai for his hospitality during my visit to Japan and showing me so much of Japanese culture.

Finally I would like to thank my mum, dad, brother and the rest of my family for all their help and support in my time at Bath and for putting up with all of my occasionally occurring bad moods.

I have almost spent 10 years of my life in Bath and it has become a second home to me, when it comes the time to leave this place I shall miss it greatly.

Abbreviations

AD	asymmetric dihydroxylation
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
°C	degrees Celsius
CD	circular dichroism
CDA	chiral derivatization agent
C_6D_6	deuterated benzene
$CDCl_3$	deuterated chloroform
CFTA	α-cyano-α-fluorophenylacetic acid
CSA	chiral solvating agent
δ	chemical shift in parts per million
Δδ	change in chemical shift
DCC	*N*,*N*'-dicyclohexylcarbodiimide
d.e.	diastereomeric excess
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
D_2O	deuterated water
dppe	1,2-*bis*-(diphenylphosphino)ethane
d.r.	diastereomeric ratio
e.e.	enantiomeric excess
EI	electron impact
equiv.	equivalents
e.r.	enantiomeric ratio
ES	electrospray

Et	ethyl
g	gram
GC	gas chromatography
HPLC	high pressure liquid chromatography
hr	hour(s)
HRMS	high resolution mass spectrometry
Hz	hertz
I	*iso*
IR	infrared
J	coupling constant
m	meta
M	molar
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeO	methoxy
MeOH	methanol
meso	mesomeric
MHz	megahertz
min	minute(s)
mL	millilitre
mmol	millimole
mp	melting point
MPA	α-methoxyphenylacetic acid
MS	molecular sieves
m/z	mass to charge ratio
NMR	nuclear magnetic resonance

o	ortho
p	para
Ph	phenyl
ppm	parts per million
R	generic substituent
rac	racemic
rt	room temperature
^{t}	*tert*
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
UV	ultraviolet
ν	wavenumber

Abstract

Three simple protocols for the determination of the enantiomeric excess of chiral amines, hydroxylamines and diols have been developed utilising boronic acid templates. In Chapter 1 some of the existing methods for determining the enantiomeric excess of chiral substrates have been reviewed including the use of chiral solvating agents, chiral derivatization agents, chiral gas chromatography, chiral HPLC, circular dichroism, UV-visible spectroscopy and fluorescence spectroscopy.

In Chapter 2 the previous work by the Bull-James group is discussed along with the cited uses of our three-component derivatization protocols for determining the enantiomeric excess of chiral amines and diols. The syntheses of a range of α-arylglycines are described and their optical purities determined by a simple ^{1}H NMR derivatization protocol.

In Chapter 3 the first reported chiral derivatization protocol for determining the enantiomeric excess of chiral hydroxylamines by ^{1}H NMR spectroscopy has been developed by formation of nitrono-boronate ester complexes whose structures have been confirmed by X-ray crystallography. A range of chiral hydroxylamines have been prepared and the mechanism for the conversion of a chiral amine to its corresponding hydroxylamine has been proposed by analysis of the side product formed during the final reaction step converting an oxaziridine to the desired hydroxylamine.

In Chapter 4 the Horeau Principle is discussed and its applications in the literature reviewed. A new derivatization protocol based on this principle has been developed employing an achiral boronic acid template to form diastereomeric dimeric boronate complexes by its reaction with two equivalents of a chiral diol. The scope and limitations of this protocol have been determined and molecular modelling has been used to explain the differences in diastereomeric resonances observed for the boronate complexes formed.

Contents

1 **Methods for the Determination of Enantiomeric Excess: A Review of the Literature** 1

1.1 Introduction 1

1.2 Methods for the Determination of Enantiomeric Excess 4

1.2.1 *Chiral Solvating Agents* 4

1.2.2 *Chiral Derivatization Agents* 14

1.2.3 *Chiral Gas Chromatography* 32

1.2.4 *Chiral HPLC* 35

1.2.5 *Polarimetry and Circular Dichroism* 39

1.2.6 *Ultraviolet-visible and Fluorescence Spectroscopy* 46

2 **A Simple Protocol for NMR Analysis of the Enantiomeric Purity of α-Arylglycines** 51

2.1 Introduction 51

2.2 Previous Work by the Group 58

2.3 Results and Discussion 78

2.3.1 *Auxiliary Controlled Strecker Syntheses of α-Arylglycines* 78

2.4 Conclusions 91

3 **A Simple Protocol for NMR Analysis of the Enantiomeric Purity of Chiral Hydroxylamines** 92

3.1 Introduction 92

3.2 Results and Discussion 95

3.2.1 *Synthesis of Chiral Hydroxylamines* 95

3.2.2 *Development of a Protocol to Determine the Enantiomeric Excess of Chiral Hydroxylamines* 102

3.3 Conclusions 111

4 **A Simple Protocol for NMR Analysis of the Enantiomeric Purity of Chiral Diols Using an Achiral Diboronic Acid Template** 112

4.1 Introduction 112

4.1.1 *The Horeau Principle* 112

4.1.2 *Enantiomeric Excess Determination by the Horeau Method* 116

4.1.3 *Enantioenrichment of Intermediates during Synthesis* 122

4.1.4 *Enantioenrichment of Chiral Substrates* 129

4.2 Results and Discussion 139

4.2.1 *Synthesis of Chiral Diols Using Sharpless Dihydroxylation Reaction* 146

4.2.2 *Scope and Limitations of the Chiral Derivatization Protocol* 147

4.2.3 *Attempted Improvements of $\Delta\delta$ Values* 150

4.2.4 *Scalemic Sampling Studies* 153

4.2.5 *Molecular Modelling to Explain Differences in Diastereomeric Resonances* 154

4.3 Conclusions 157

5 **Experimental** 158

5.1 General Experimental Details 158

5.2 General Procedures for Chapter 2 159

5.2.1 *General Procedure 1: (S,S)-α-Amino Nitrile Hydrochloride Formation* 159

5.2.2 *General Procedure 2: (S)-α-Arylglycine Hydrochloride Formation* 160

5.2.3 *General Procedure 3: Determination of the Enantiomeric Excess of (S)-α-Arylglycine Hydrochlorides* 160

5.3 Synthesis of Compounds in Chapter 2 160

5.4 General Procedures for Chapter 3 169

5.4.1 *General Procedure 4: Chiral Hydroxylamine Formation* 169

5.4.2 *General Procedure 5: Determination of the Enantiomeric Excess of Chiral Hydroxylamines* 170

5.5 Synthesis of Compounds in Chapter 3 170

5.6 General Procedures for Chapter 4 185

5.6.1 *General Procedure 6: Dihydroxylation of Alkenes* 185

5.6.2 *General Procedure 7: Determination of the Enantiomeric Excess of Chiral Diols* 185

5.7 Synthesis of Compounds in Chapter 4 186

6 **Appendix** 195

7 **References** 257

1 Methods for the Determination of Enantiomeric Excess: A Review of the Literature

1.1 Introduction

Chirality is prevalent throughout chemistry and biology and compounds can be synthesised in an enantiomerically enhanced or pure form by a range of methods such as enantioselective catalysis[1-3] and organocatalysis,[4-6] use of chiral auxiliaries,[7,8] biocatalysis[9] and chiral pool synthesis.[10] Nature itself makes and employs chiral compounds, for example for the biosynthesis of proteins using chiral amino acids.

A chiral molecule is one which is non-superimposable upon its mirror image. Each of the enantiomers of a chiral compound has identical physical, chemical and spectroscopic properties when in an achiral environment, but often behave differently when in a chiral environment. Biologically active molecules such as proteins and sugars are chiral polymers built from a series of chiral building blocks. As a result, enantiomers of chiral compounds can have drastically differing biological activity, with the case of thalidomide perhaps being the most famous of examples.[11] As a result of this, chiral drugs are now required to ideally be administered in an enantiomerically pure form and there is therefore a high demand for asymmetric methodologies and for techniques of rapidly determining the enantiopurity and absolute configuration of chiral compounds.[12]

There are a number of different types of chirality with point chirality being the most common. Molecules with point chirality normally have one or more stereogenic carbon centres which are attached to four different substituents. The absolute configuration of a point chiral centre is determined by using the Cahn-Ingold-Prelog rules and given a stereodescriptor based on the priorities of atoms about the centre assigned according to atomic number.[13] When a viewpoint is taken where the lowest priority group is directed away from the viewer then, a priority which rotates to the right is denoted as rectus (*R*), with its opposite enantiomer denoted as sinister (*S*) (Figure 1).

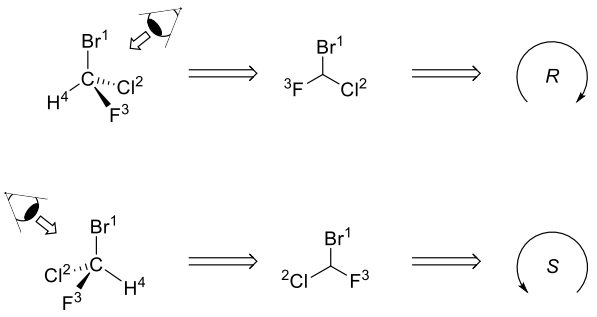


Figure 1 - Assignment of absolute configuration according to the Cahn-Ingold-Prelog rules

Molecules without stereogenic centres can also be chiral in special cases due to axial chirality. Axial chirality is commonly observed in allenes and biaryl systems such as BINOL. Due to the orbital alignment of their π-bonds, the terminal substituents of allenes containing even numbers of connected double bonds are held at 90° to each other and can be viewed down its axis as a pseudo tetrahedron (Figure 2). Since these compounds can be viewed as pseudo tetrahedral structures their stereochemistry can also be assigned by application of the Cahn-Ingold-Prelog rules.

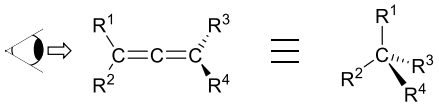


Figure 2 - Chiral allene viewed as a pseudo tetrahedron

Biaryl structures such as BINOL also possess axial chirality which arises from hindered rotation about the bond connecting the two ring systems. Due to the locked geometry about this axis, the two mirror images of the molecule are not superimposable and the molecule is therefore chiral. Its stereochemistry can be assigned by viewing the molecule along this chiral axis and assigning priority to the

substituents connected to either end of the axis. In this case, the priority of the nearest groups are assigned first, with its absolute configuration once again assigned based on the direction in which the priories rotate (Figure 3).

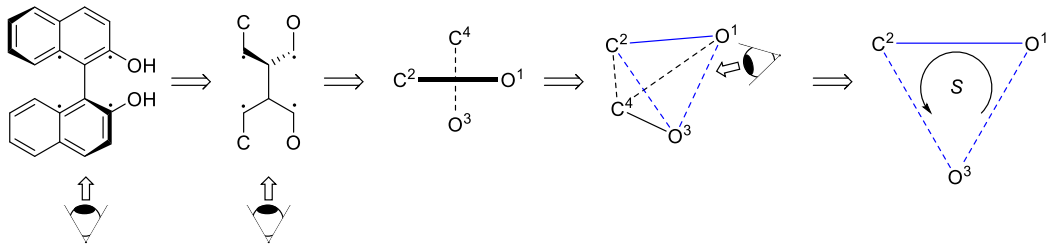


Figure 3 - Assignment of the chirality of (*S*)-BINOL

Amines and phosphines with three different substituents become chiral due to their lone pair acting as a fourth substituent. However, amines exhibit no optical activity as the lone pair of amines invert too rapidly to make either enantiomer isolable unless the nitrogen atom is part of a rigid cyclic molecule. The energy of inversion of phosphines and their oxides is very high, making their enantiomers isolable. Sulphur, phosphorus and nitrogen oxides can also exhibit this type of optical activity (Figure 4).

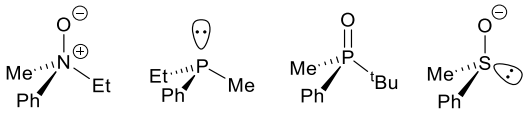


Figure 4 - Chirality at nitrogen, phosphorus and sulphur

The ability to discern the chirality and enantiopurity of a compound is important to the modern synthetic chemist. Chemists have a constant need to measure enantiopurity for such purposes as determining the effectiveness of a chiral

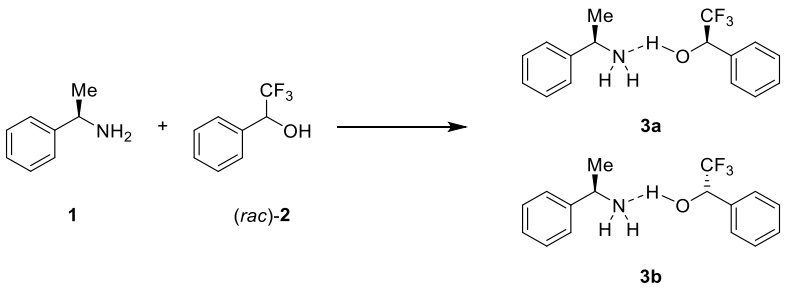
auxiliary,[14] or when screening large numbers of asymmetric catalysts.[15] Techniques to determine enantiomeric excess (*e.e.*) quickly such as derivatization with chiral auxiliaries,[16,17] chiral chromatography[18] and spectroscopic analysis[15,19] and NMR spectroscopy[20,21] are therefore highly desired. This thesis deals with the development of new NMR spectroscopic methods to determine the enantiomeric excess of chiral amines, hydroxylamines and diols. Consequently, the remainder of this chapter will highlight some of the major methods employed for determining the enantiomeric excess of chiral compounds.

1.2 Methods for the Determination of Enantiomeric Excess

1.2.1 Chiral Solvating Agents

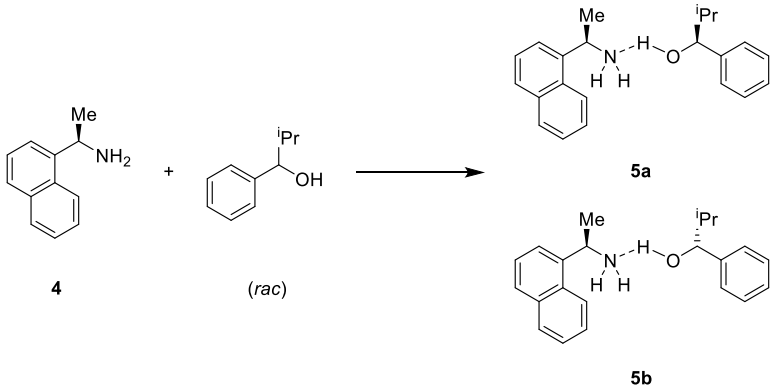
Chiral solvating agents form *in situ*, diastereomeric complexes with chiral substrates. These complexes are transient in nature unlike the long-lived covalent complexes formed with Chiral Derivatization Agents (CDAs).

In 1966, Pirkle reported the first use of a chiral solvating agent to determine the enantiomeric excess of a chiral alcohol.[22] It was discovered that enantiomerically pure α-methylbenzylamine **1** formed reversible diastereomeric complexes **3a** and **3b** with (*rac*)-2,2,2-trifluoro-1-phenylethanol **2** through hydrogen bonding interactions between the amine group of the α-methylbenzylamine and the hydroxyl proton of the alcohol (Scheme 1). Inspection of the ^{19}F NMR spectrum of a mixture of α-methylbenzylamine **1** and (*rac*)-2,2,2-trifluoro-1-phenylethanol **2** also showed distinct diastereomeric resonances for the fluorine atoms of the CF_3 group.



Scheme 1 – The first reported chiral solvating agent for alcohols reported by Pirkle

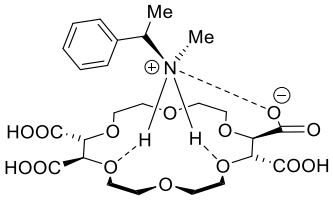
A further publication by Pirkle *et al.* demonstrated how enantiodiscrimination could also be performed using ^{1}H NMR spectroscopy by using 1-(1-naphthyl)-ethylamine **4** as a chiral solvating agent (Scheme 2). In this case, baseline separated methyl resonances for the diastereomeric *iso*-propyl groups were observed in the ^{1}H NMR spectrum of the resultant mixture of diastereomeric complexes **5a** and **5b**.



Scheme 2 - 1-(1-Naphthyl)-ethylamine 4 used as a ^{1}H NMR chiral solvating agent

For the enantiomeric discrimination of chiral amines, crown ethers are often used as chiral solvating agents. In particular, 18-crown-6 type ethers have the correct geometry to associate with protonated primary amines as the oxygen atoms in the crown ether can form hydrogen bonds with the ammonium protons. Wenzel *et al.*

have reported how (18-crown-6)-2,3,11,12-tetracarboxylic acid is a useful agent for the discrimination of secondary chiral amines.[23] Wenzel proposed that secondary amines protonated by one of the carboxylic acid groups on crown ether **6** would hydrogen bond with two of the ether oxygens in the ring structure, thus forming an ionic interaction between the ammonium nitrogen and the deprotonated carboxylic acid (Figure 5).



6

Figure 5 – Complexation between (18-crown-6)-2,3,11,12-tetracarboxylic acid and a chiral secondary amine

For the case of the addition of the crown ether to (*rac*)-*N*-methyl-α-methylbenzylamine, the ^{1}H NMR spectrum of the resultant mixture of diastereomeric complexes showed pairs of resonances for the diastereomeric *N*-methyl and *C*-methyl moieties of *N*-methyl-α-methylbenzylamine. Scalemic sampling (enrichment of one enantiomer over the other) proved that these pairs of resonances were due to enantiodiscrimination rather than solvent effects. Wenzel also noted that it was possible to increase baseline separation of these signals by addition of further amounts of crown ether up to a 2:1 ratio of crown ether:secondary amine. This method was shown to be effective for the enantiodiscrimination of a range of chiral secondary amines, with further publications extending this methodology to include chiral piperidines, piperazines[24] and pyrrolidines.[25]

Pérez-Trujillo *et al*. have reported the use of chiral solvating agents to determine the enantiomeric excess of a number of pharmaceutical compounds.[26] Two anthracene

based compounds **7** and **8** were shown to form diastereomeric complexes with the pharmaceuticals carvedilol **9**, fluoxetine **10**, and *N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **11** which were readily distinguishable by ^{1}H NMR spectroscopy (Figure 6).

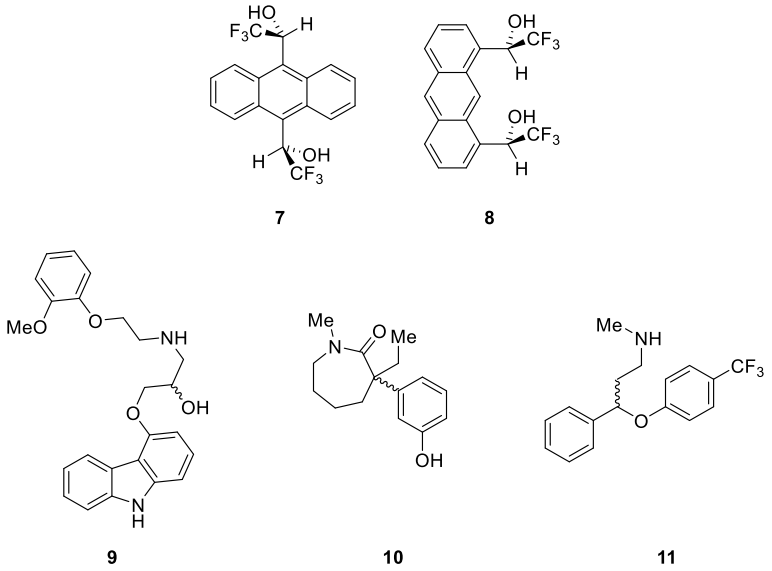
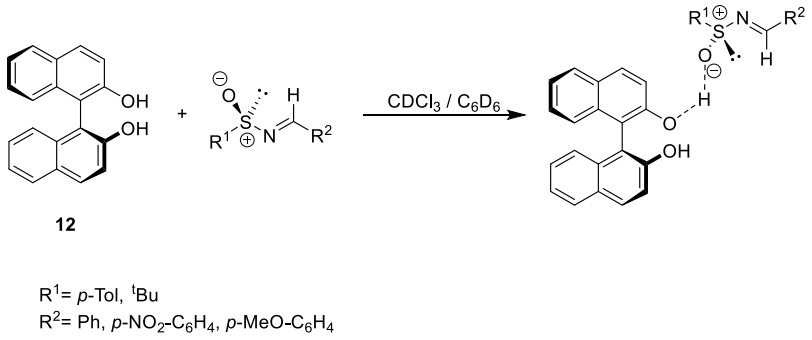


Figure 6 – Chiral anthracene solvating agents 7 and 8 used to determine the enantiopurity of the pharmaceuticals carvedilol 9, fluoxetine 10 and *N*-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine 11

Upon mixing of CSA **7** with carvedilol **9**, the resultant ^{1}H NMR spectrum showed very good degrees of signal splitting for the methoxy protons of the carvedilol, with accurate integrations of diastereomeric protons easily obtainable. Similar results were obtained for the mixture of CSA **8** with **11** and it was noted that baseline separation of the *C*-methyl resonance was further improved by addition of up to 2.5 equivalents of **8**. Finally, the (*S*,*S*)-analogue of CSA **7** was shown to be effective for determining the enantiomeric excess of fluoxetine **10**.

Kawęcki *et al.* have reported the use of BINOL as a chiral solvating agent for sulfinimines.[27] Substituted *t*-butyl and *p*-tolylsulfinyl derivatives of sulfinimines were mixed with varying amounts of (*S*)-BINOL **12** in $CDCl_3$ (Scheme 3) and a pair

of baseline resolved signals for the imine proton were seen when racemic sulfinimine was employed.

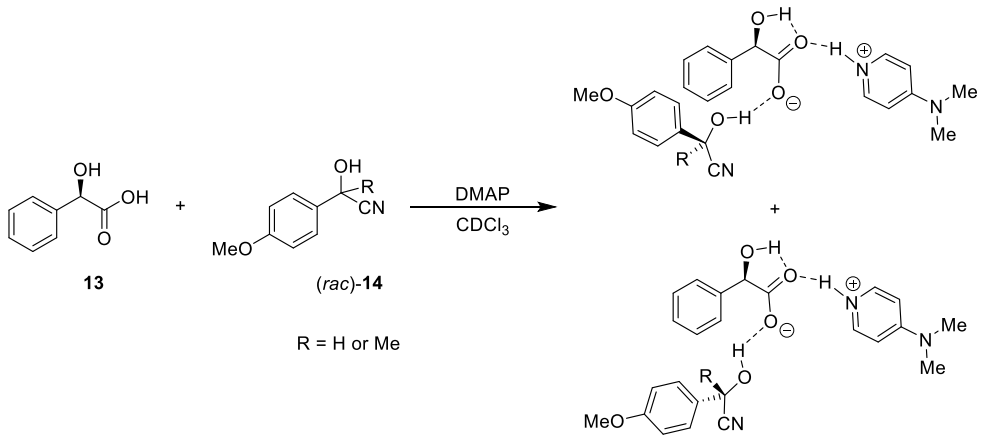


Scheme 3 - Use of BINOL 12 as a chiral solvating agent for sulfinimines

In all cases, it was reported that an increase in the amount of (*S*)-BINOL added above a 1:1 molar ratio increased the separation between the pair of diastereomeric imine resonances, with up to 10.5 equivalents of (*S*)-BINOL being needed to achieve maximum separation. However, additions of large amounts of chiral solvating agent were shown to, on occasion, cause line broadening in the ^{1}H NMR spectra. This problem could be resolved by using C_6D_6 as solvent, which in some cases, produced $\Delta\delta$ (the difference in ppm between the shifts of two diastereomeric protons in the ^{1}H NMR spectrum) values twice those observed in $CDCl_3$. In all cases, the diastereomeric imine protons were sufficiently well resolved to provide integration accurate enough to determine enantiomeric excess to within 1% of true values. It was noted that the sulfinimine resonance was an excellent diagnostic tool since it was always a singlet, and so baseline separation could be achieved at smaller $\Delta\delta$ values than for broader multiplet resonances which can potentially overlap.

Jolly *et al.* have published an extensive study into the use of mandelic acid **13** as a chiral solvating agent for the determination of the enantiomeric excess and absolute configuration of chiral cyanohydrins **14**.[28] It was reported that it was possible to determine the enantiomeric excess for both aldocyanohydrins and ketocyanohydrins

by addition of equimolar amounts of mandelic acid **13** and DMAP to the relevant cyanohydrin in $CDCl_3$ (Scheme 4).



Scheme 4 - Formation of diastereomeric complexes for determining the enantiomeric excess of cyanohydrins

For aldocyanohydrins the α-proton was found to be diagnostic since, in all cases, a pair of baseline resolved resonances were seen for each diastereomer in the ^{1}H NMR spectra of the resultant mixtures. These resonances were sufficiently separated so that no problems were encountered when the resonance for the α-proton was a multiplet rather than a simple singlet, and thus accurate integration was possible to determine the enantiomeric excess for all aldocyanohydrins. For the case of ketocyanohydrins, where no α-proton is present, other protons in the complexes were used to determine enantiomeric excess, with the presence of α-methyl protons in the chiral analyte being particularly diagnostic. Conversely, it was later discovered by Jolly *et al.* that a chiral cyanohydrin, such as 4-methyoxymandelonitrile could be used to determine the enantiomeric excess of chiral carboxylic acids.[29]

In 2011, Sirit *et al.* reported four phthalimide based chiral solvating agents **15-18** for determining the enantiomeric excess of chiral carboxylic acids (Figure 7).[30]

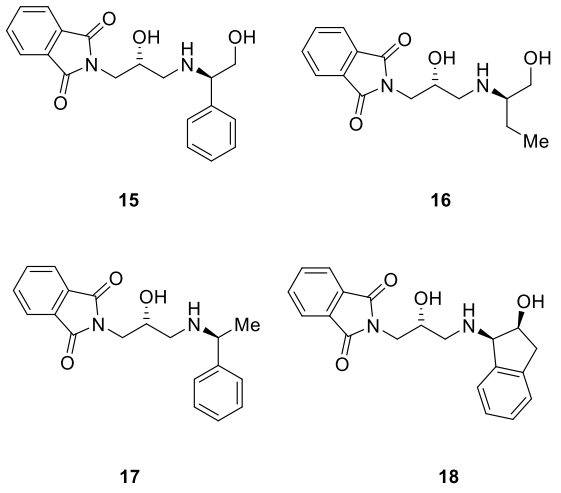


Figure 7 – Phthalimide based chiral solvating agents for determining the enantiomeric excess of carboxylic acids

The four chiral solvating agents **15-18** were prepared from (*R*)-*N*-(2,3-epoxypropyl)phthalimide and the appropriate chiral amine or amino alcohol. They were then mixed with a number of chiral carboxylic acids in $CDCl_3$ and the ^1H NMR spectra obtained. These spectra showed that, for all solvating agents, splitting was seen for a number of resonances of the carboxylic acid. In particular, a pair of diastereomeric resonances were observed for the methine proton of mandelic acid, which were baseline separated enough that they could be accurately integrated in order to determine enantiomeric excess. However, this approach only resulted in small separations for the resonances of diastereomeric protons of certain types of carboxylic acid. Solvating agents **15** and **17** showed the largest chemical shift differences between diastereomeric protons for 2-chloromandelic acid of varying enantiomeric excess. Integration of the diastereomeric methine resonances in the ^1H NMR spectra showed that enantiomeric excess could be determined to within 1% of the true value. However, this required that diastereomeric proton resonances were sufficiently baseline separated, which was not the case for all carboxylic acids investigated.

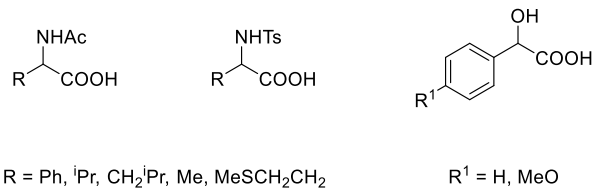


Figure 8 – The range of chiral carboxylic acids resolved by macrocycles 15 and 17

Two further chiral solvating agents for the enantiopurity determination of carboxylic acids have been reported recently by Ai *et al.*.[31] The ^{1}H NMR spectra of a range of carboxylic acids and *N*-protected amino acids were obtained after mixing them with one equivalent of macrocycle **19** or **20** (Figure 9), with pairs of baseline resolved peaks corresponding to each of the diastereomeric complexes being observed in the ^{1}H NMR spectrum.

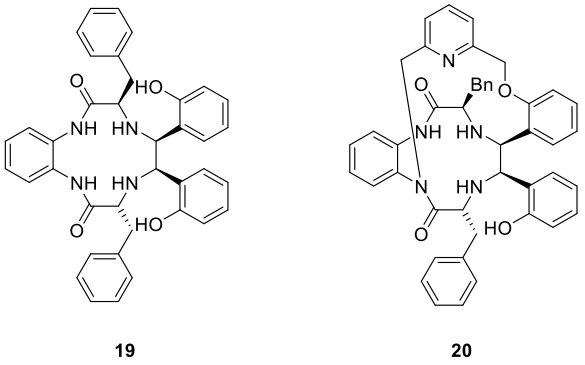
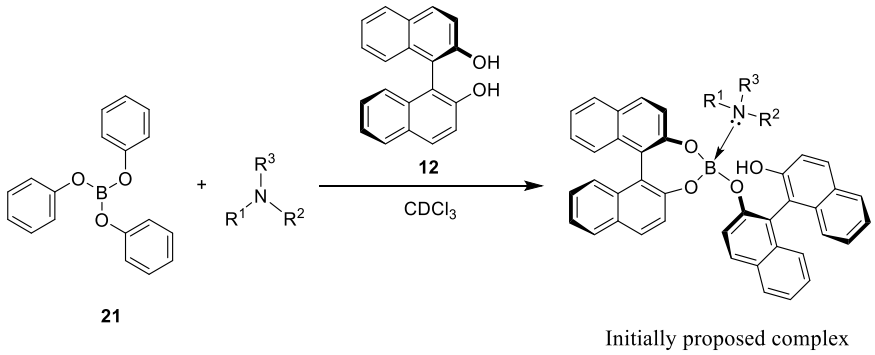


Figure 9 – Macrocycles 19 and 20 employed by Ai to determine the enantiomeric excess of chiral carboxylic acids and amino acids

In the majority of cases the α-proton was the most useful diagnostic resonance in the ^{1}H NMR spectra with macrocycle **19** proving to be the most effect chiral solvating agent, affording resolved resonances for almost every chiral compound investigated. Scalemic sampling demonstrated that the use of both these macrocycles for

determining the enantiopurity of chiral carboxylic acids and *N*-protected amino acids produced accurate results within 2% of known *e.e.* values.

Recently, Suryaprakash *et al.* have demonstrated a method for determining the enantiomeric excess of chiral amines and amino alcohols by formation of a complex between a boronic ester and a chiral substrate.[32] It was reported that mixing triphenylborate **21** and a chiral amine for 45 seconds followed by addition of (*R*)-BINOL **12** led to formation of an N-B complex between a boronate ester and the chiral amine (Scheme 5).

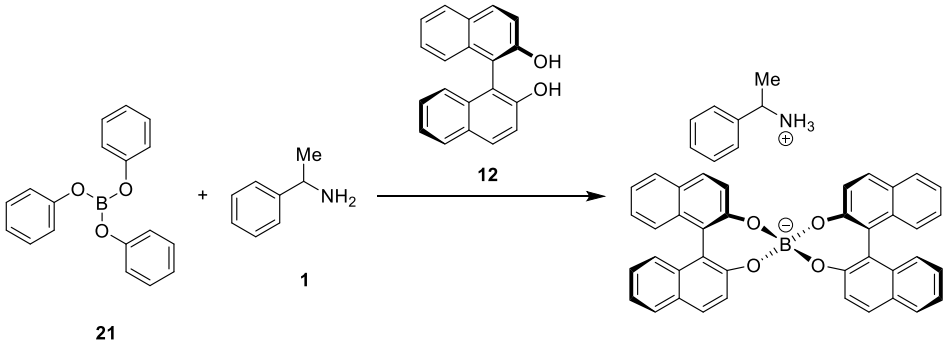


Scheme 5 – The use of a BINOL based chiral solvating agent for determining the enantiomeric excess of chiral amines

A range of chiral primary, secondary, tertiary amines and amino alcohols could be discriminated upon complexation by ^{1}H NMR spectroscopy. At least two diastereomeric pairs of proton resonances could be used to determine enantiomeric excess for each chiral substrate with enantiomeric excess calculated to within 2% of the known values of starting substrate.

Suryaprakash *et al.* then turned their attention to determining the true structure of the complexes formed in this method.[33] DFT calculations and analysis of the ^{11}B NMR spectrum for the complex formed between triphenylborate **21**, (*R*)-BINOL **12** and α-methylbenzylamine **1** led to the suggestion that the structure was not in fact

the N-B complex suggested previously (Scheme 5), but an ion pair complex formed between a boronate anion and an ammonium cation (Scheme 6).



Scheme 6 – Chiral salt formation that enables the enantiomeric excess of chiral amines to be determined

BINOL has also been recently reported to be a useful chiral solvating agent for determining the enantiomeric excess of crispine A **22** (Figure 10) and related amines by Yuste *et al.*.[34]

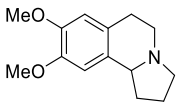


Figure 10 – Structure of (*rac*)-crispine A 22

It was found that a mixture of five equivalents of (*R*)- or (*S*)-BINOL with racemic crispine A **22** in $CDCl_3$ led to differing signals in the ^1H NMR spectrum for each of the transient diastereomeric complexes formed in the mixture. The aryl and methoxy protons of crispine proved particularly useful for enantiopurity determination as their resonances were completely baseline resolved. It was also discovered that

using C_6D_6 as solvent provided a larger chemical shift difference between the pairs of methoxy proton resonances than when $CDCl_3$ was employed.

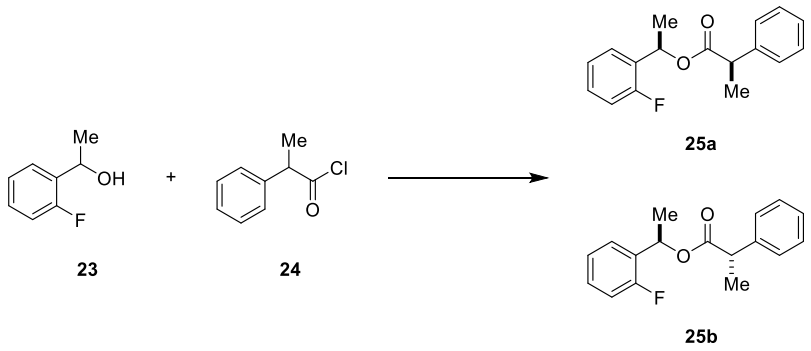
Chiral solvating agents are a convenient tool with which to determine the enantiomeric excess of chiral substrates. They are experimentally simple to use, reactions can be performed in an NMR tube and no problems arising from kinetic resolution and racemisation occur. However, the chemical shift differences seen in the NMR spectra obtained from these experiments can often be very small, making accurate integration problematic at times. It has been shown that chemical shift differences can be improved by addition of excess amounts of chiral solvating agents; however, this can be a disadvantage if the chiral solvating agent is expensive, or has limited solubility.

1.2.2 Chiral Derivatization Agents

Chiral derivatization agents are chiral auxiliaries that form long-lived diastereomeric covalent complexes after reaction with a chiral substrate. This method of stereodiscrimination exploits the fact that, whereas the chemical shifts of enantiomeric protons in NMR spectra are the same, the chemical shifts of diastereomeric protons are often different. A significant advantage of chiral derivatization agents is that generally, the chemical shift differences observed are far greater than those observed using chiral solvating agents.

However, it is necessary to use an enantiomerically pure derivatizing agent, or inaccurate enantiomeric excesses may be calculated. Kinetic resolution can also cause problems as the process relies on statistical formation of diastereomeric complexes based on the enantiomeric excess of the chiral substrate. If kinetic resolution occurs and one diastereomer is formed preferentially over another then an inaccurate value for enantiomeric excess will be calculated.

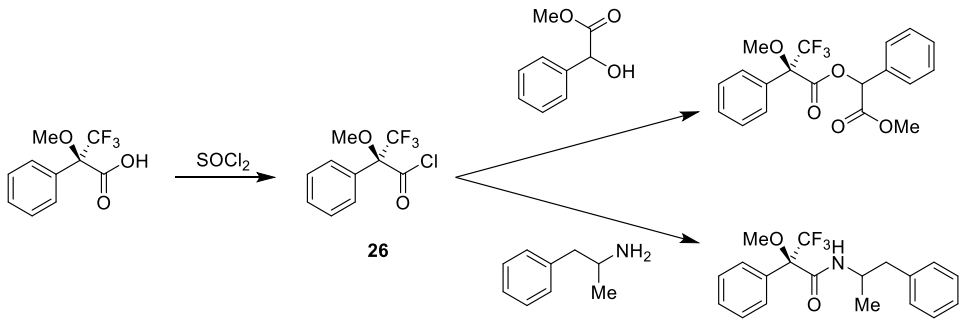
The first chiral derivatization agent for NMR spectroscopic analysis was published by Raban in 1965 through reaction of 1-(*o*-fluorophenyl)-ethanol **23** and 2-phenylpropanoyl chloride **24** (Scheme 7).[35]



Scheme 7 – Raban's chiral derivatization agent for alcohols, first published in 1965

Upon inspection of the ^{1}H NMR spectrum of the diastereomeric mixture formed in the reaction, Raban noted that the methyl resonances for each diastereomer were resolved and accurate integration was able to determine the diastereomeric ratio (*d.r.*) of compound **25** as 68:32. This was confirmed to be in excellent agreement with the value of 67:33 obtained from analysis *via* gas chromatography. Raban also postulated that the use of ^{19}F NMR spectroscopy would be effective for determining the enantiomeric excess of amino acids by derivatization with chiral *N*-trifluoroacyl transfer reagents.

Some of the most commonly employed chiral derivatization agents are those reported by Mosher and Trost. In 1969, Mosher first reported the use of α-methoxy-α-trifluoromethylphenylacetic acid (Mosher's acid) chloride **26** as a chiral derivatization agent for determining the enantiomeric excess of alcohols and amines using ^{1}H NMR spectroscopy (Scheme 8).[16]

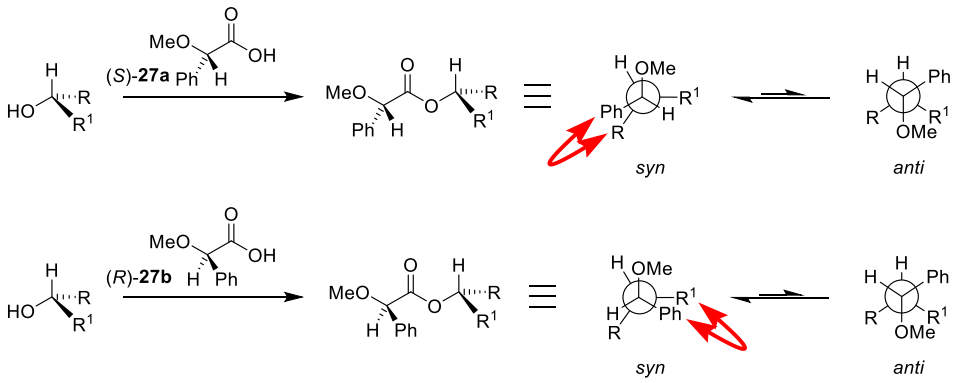


Scheme 8 – Mosher's acid 26 as a chiral derivatization agent for alcohols and amines

During initial studies, Mosher's method was shown to determine enantiomeric excess within 1% of known values for a range of secondary alcohols and amines. Mosher's acid proved to be a more successful chiral derivatization agent than the previously reported α-methoxyphenylacetic acid **27**, which was found to undergo racemisation by exchange of its relatively acidic α-proton during derivatization of sterically hindered alcohols.[36] Mosher's acid contains no such α-proton and is therefore unable to undergo racemisation *via* this enolisation mechanism. The work of Riguera would then show conformational analysis of the ester and amide derivatives formed and rationalise the diastereomeric resonances seen in the ^{1}H NMR spectra of derivatized substrates.

Since its initial publication this approach has proven to be particularly popular for determining enantiomeric excess and a number of groups have used molecular modelling and NMR studies to show that both α-methoxyphenylacetic acid and Mosher's acid ester and amide derivatives exist in solution as an interconverting mixture of *syn*-periplanar and *anti*-periplanar conformers in equilibrium, with each conformer exhibiting its own anisotropic shielding effects.[37] Riguera reported that the phenyl groups of the lowest energy *syn*-periplanar conformers of α-methoxyphenylacetic acid ester derivatives are orientated to maximise shielding effects, but that the *anti*-periplanar conformers are less populated and exhibit weaker shielding effects. As a result, Riguera suggested a simple empirical model to rationalise the chemical shift differences of diastereomeric α-methoxyphenylacetic acid ester derivatives that considers the shielding effects of the lowest energy *syn*-

periplanar conformer, and ignores contributions from the minor *anti*-periplanar conformers (Scheme 9).



Scheme 9 - Newman projections of the *syn*- and *anti*-periplanar conformers of α-methoxyphenylacetic acid 27 diastereomeric esters, red arrows denote shielding effects

In this model, the R-substituent of the *syn*-periplanar diastereomeric ester conformer formed between (*S*)-α-methoxyphenylacetic acid **27a** and a chiral alcohol is anisotropically shielded by the aromatic ring of the acid fragment. However, in the diastereomer incorporating (*R*)-α-methoxyphenylacetic acid **27b** the phenyl group shields the R^1-substituent and causes a relative shift of its resonance in the ^{1}H NMR spectrum to a higher δ value. It was determined that decreasing the temperature of the NMR probe resulted in a shifting of the bias of equilibrium towards the more stable *syn*-periplanar conformer, thus increasing the diastereomeric shift difference in the ^{1}H NMR spectrum.

For the case of amide derivatives of α-methoxyphenylacetic acid **27**, Riguera reported that the most stable conformer adopted an *anti*-periplanar configuration, resulting in a predictive model that is the reverse of that reported for chiral alcohols.[38] The difference in conformation between amide and ester derivatives was proposed by Trost to be due to an intramolecular hydrogen bond between the amide proton and the methoxy group (Figure 11).[17]

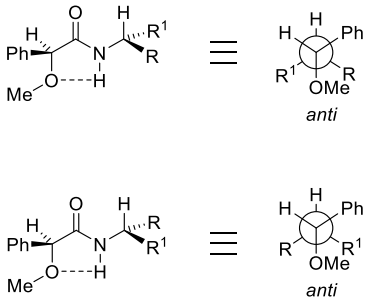
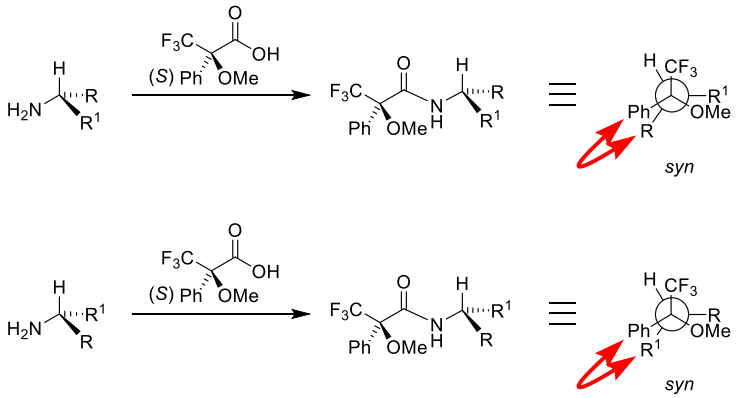


Figure 11 - A*nti*-periplanar conformers for amides of α-methoxyphenylacetic acid 27 formed due to intramolecular hydrogen bonding between the amide proton and methoxy group

Similar conformational investigations have also been reported for Mosher's acid to determine the enantiomeric excess of chiral amines by formation of amide derivatives.[36] Mosher's amide derivatives have been shown to exist as a mixture of three different conformers in solution. As has been reported for the derivatives of α-methoxyphenylacetic acid and chiral alcohols, the phenyl groups of the lowest energy *syn*-periplanar conformers are in an orientation which maximises shielding effects, whilst the two less populated *anti*-periplanar conformers are in orientations with weaker shielding effects. For the lowest energy conformer, the R-substituent of the amide product is in a *syn*-periplanar conformation to the anisotropically shielding phenyl ring (Scheme 10). For the derivative employing the opposing enantiomer of the amine it is the R^1-substituent that is anisotropically shielded by the aromatic ring, which leads to a relative upfield shift of its resonances in the ^1H NMR spectra.[39]

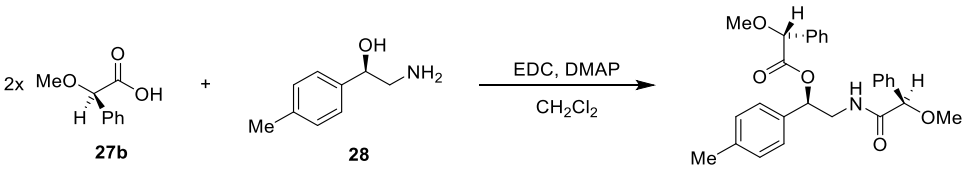


Scheme 10 - Conformational analysis of diastereomeric amide derivatives formed between Mosher's acid and a chiral amine

The difference in these anisotropic effects and the resultant difference in chemical shifts of the two diastereomers formed make both α-methoxyphenylacetic acid and Mosher's acid very useful reagents for determining the enantiomeric excess of chiral amines. It has also been reported that consideration of the sign of the Δδ values obtained can be used to predict the absolute configuration of a chiral amine by consideration of the conformational model described above.[40] Derivatization of an enantiopure chiral amine of unknown configuration with both enantiomers of Mosher's acid will result in a pair of diastereomers with differing anisotropic effects and therefore different chemical shifts for their R and R^1 substituents. Derivatization of the amine with the (*S*)-enantiomer of Mosher's acid will result in an upfield shift in the resonance for the R-substituent in the ^{1}H NMR spectrum since it will be anisotropically shielded by the phenyl ring of the acid fragment. Conversely, derivatization of the amine with the (*R*)-enantiomer of Mosher's acid will result in the resonance for the R^1 substituent being shifted upfield due to anisotropic shielding by the aromatic ring. With this model in mind the sign of the Δδ value can then be used to predict the absolute configuration of the chiral amine. Models have since been presented to determine the absolute configuration of secondary cyclic amines.[41,42]

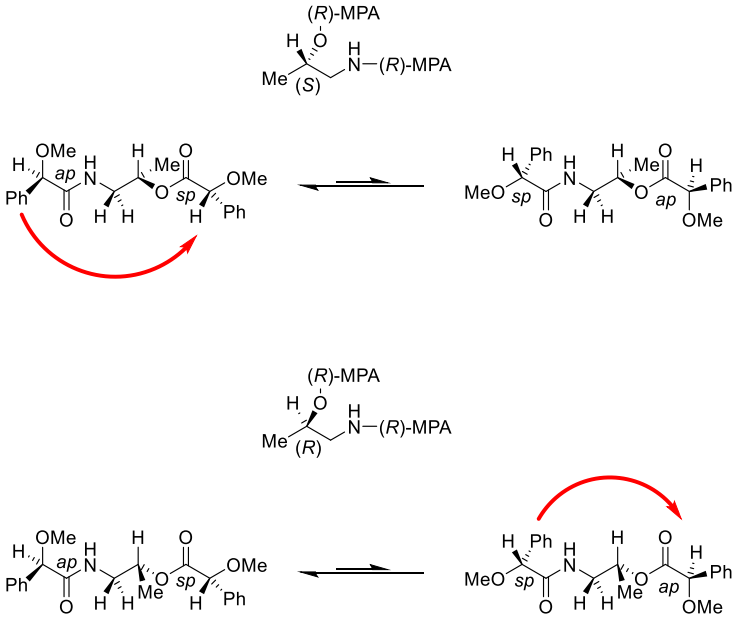
Similar conformational models have also been developed by Riguera for the application of α-methoxyphenylacetic acid as a chiral derivatization agent for amino

alcohols.[43,44] Here, two equivalents of either the (*R*)- or (*S*)- enantiomer of the derivatization agent react with the amino alcohol; one with the amine moiety and one with the alcohol functionality (Scheme 11).



Scheme 11 - Derivatization of (*R*)-2-amino-1-(*p*-tolyl)ethan-1-ol 28 with two equivalents of (*R*)-α-methoxyphenylacetic acid 27b

The absolute configuration of the amino alcohol can then be determined by ^{1}H NMR spectroscopic analysis of the resultant derivatization product and consideration of the conformational model.[45] Once again, Riguera noted that for the amide unit of the derivatized amino alcohol the major conformer is *anti*-periplanar, whilst for the ester unit the *syn*-periplanar conformer dominates.



Scheme 12 - Conformational equilibrium for *bis*-(*R*)-α-methoxyphenylacetic acid derivatives of (*S*)-and (*R*)-1-aminopropan-2-ol. Red arrows indicate the shielding effects observed in the ^{1}H NMR spectra.

Riguera reported that the absolute configuration of the chiral amino alcohol could be determined by comparing the Δδ values obtained from two ^{1}H NMR spectra, one at room temperature and the second spectrum at -60 °C. At room temperature, the α-proton of the major conformer of the ester of *bis*-(*R*)-α-methoxyphenylacetic acid with (*S*)-1-aminopropan-2-ol was shielded, whilst the α-proton of the amide was deshielded. At lower temperature, this effect is enhanced causing predictable changes to the Δδ between these two resonances. The same effect is seen for the *bis*-(*R*)-α-methoxyphenylacetic acid derivative formed from (*R*)-1-aminopropan-2-ol. A close up of the CαH and methoxy regions of the ^{1}H NMR spectrum of a derivatized amino alcohol are shown in Figure 12 which show the typical Δδ seen when α-methoxyphenylacetic acid is employed as a derivatization agent.

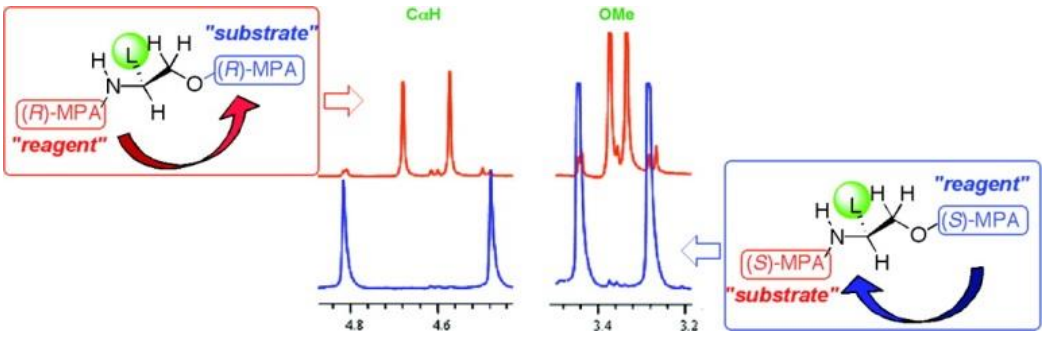
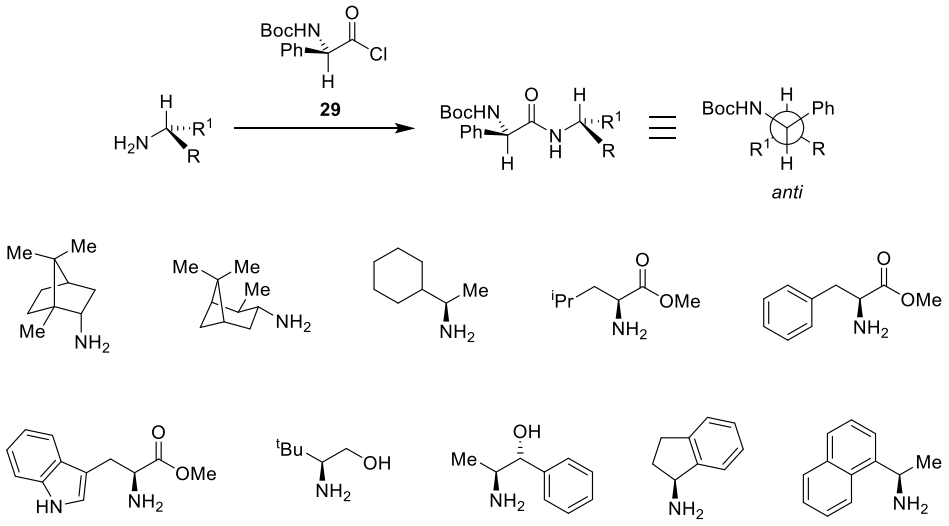


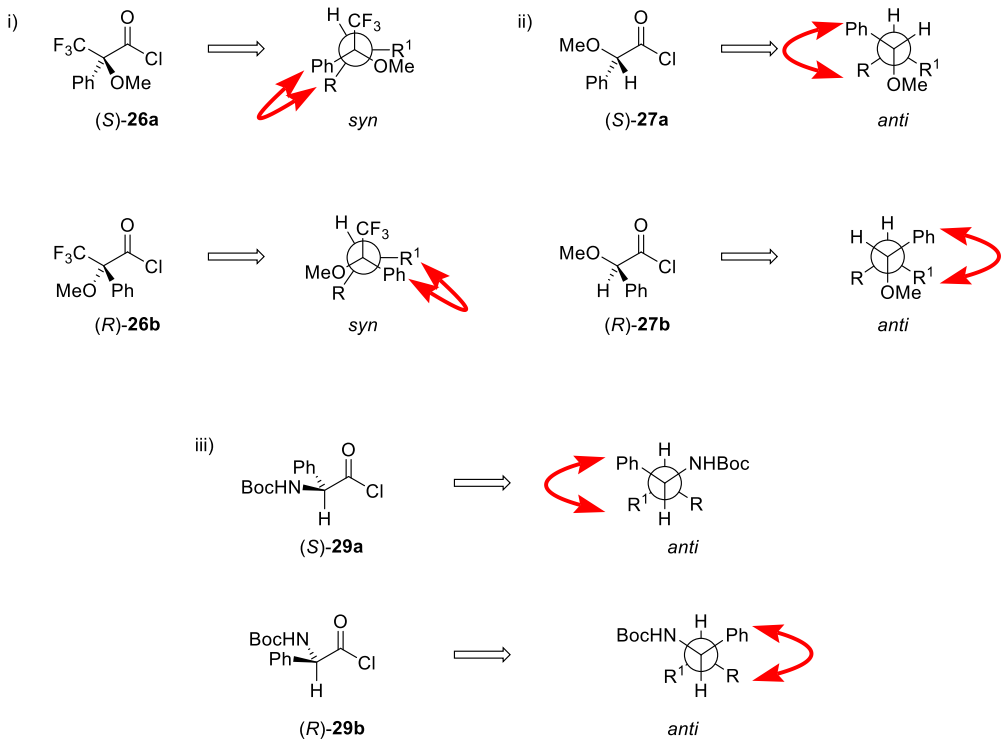
Figure 12 - Typical Δδ seen in the ^{1}H NMR for α-methoxyphenylacetic acid amide and ester derivatives[43]

N-Boc Protected phenylglycine acid chloride **29** has been reported to be an excellent chiral derivatization agent for a range of chiral amines.[46] This derivatization agent is an improvement upon α-methoxyphenylacetic acid and Mosher's acid because the Δδ values in the ^{1}H NMR spectra for the diastereomeric amide derivatives are up to three times greater in comparison to the equivalent derivatives using α-methoxyphenylacetic acid and Mosher's acid. The increase in Δδ is due to the increased anisotropic shielding effects of the aromatic ring in the major *anti*-periplanar conformer (Scheme 13).



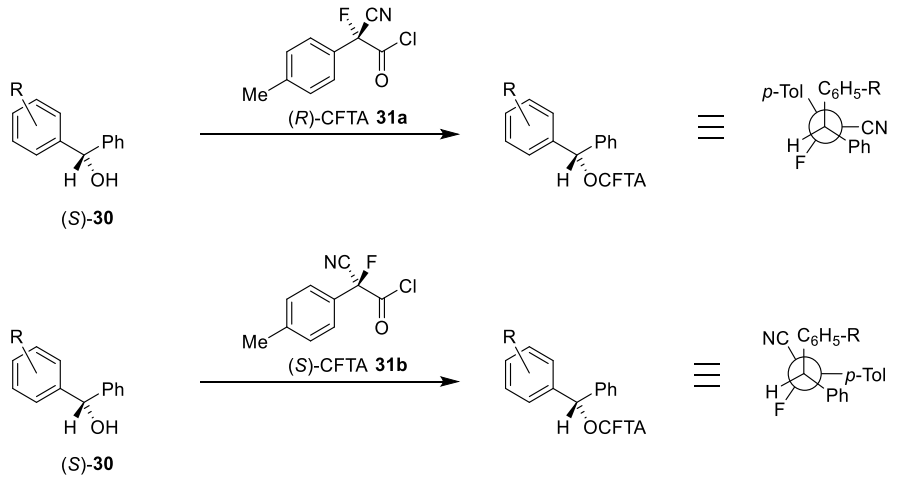
Scheme 13 - The use of *N*-Boc protected phenylglycine acid chloride 29 as a chiral derivatization agent for a wide range of primary amines

Riguera also noted that the sign of the Δδ values obtained is always the opposite of those seen for amides derived from α-methoxyphenylacetic acid and Mosher's acid. For the case of (*R*)-α-methoxyphenylacetic acid and Mosher's acid amides the R^1 substituent is anisotropically shielded by the phenyl ring in the major conformer and for (*S*)-α-methoxyphenylacetic acid and Mosher's acid amides the aromatic ring anisotropically shields the R group in the major conformer. However, when a phenyl glycine based chiral derivatization agent is employed the opposite is true, with (*R*)-phenylglycine derived amides having their R substituents anisotropically shielded by the aromatic ring, whilst for (*S*)-phenylglycine derived amides their R^1-substituents are anisotropically shielded by the phenyl ring. This results in a switch in sign of the Δδ values observed in their ^{1}H NMR spectra. The differing models for the amide derivatives formed using all three of these derivatization agents are summarised in Scheme 14.



Scheme 14 – A summary of the differences in anisotropic shielding effects of the R and R^1 substituents of amide derivatives of i) Mosher's acid chloride 26, ii) α-methoxyphenylacetic acid chloride 27 and iii) *N*-Boc protected phenyl glycine acid chloride 29. Red arrows denote anisotropic shielding effects

Takeuchi *et al.* have proposed an alternative derivatization to Mosher's acid for the determination of the enantiomeric excess of chiral secondary alcohols which boasts improved reactivity compared to α-methoxy-α-trifluoromethylphenylacetic acid. α-cyano-α-fluoro-*p*-tolylacetic acid **31** was shown to be an effective derivatization agent for determining the enantiomeric excess of chiral benzhydrols **30** and it was demonstrated that the absolute configuration of the benzhydrol could be determined from the sign of the Δδ values for the aromatic protons (Scheme 15).

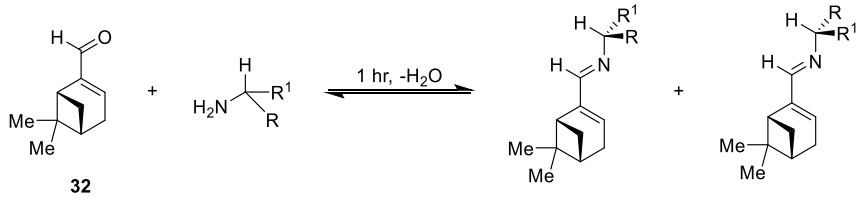


Scheme 15 - Conformational model showing shielding effects upon derivatization of (*S*)-benzhydrols with α-cyano-α-fluoro-*p*-tolylacetic acid chloride 31

The above conformational model was developed by Takeuchi for all (*S*)-benzhydrols investigated where upon derivatization with (*R*)-α-cyano-α-fluoro-*p*-tolylacetic acid **31** the substituted aromatic group of the alcohol fragment is anisotropically shielded by the *p*-tolyl group and thus appears upfield of the equivalent resonance for the underivatized alcohol. Conversely, when the (*S*)-diastereomer is formed it is the phenyl group of the alcohol fragment which is anisotropically shielded by the *p*-tolyl group and its corresponding proton resonances are shifted upfield. The CN group induces the opposite anisotropic deshielding effect and causes a downfield shift in the phenyl and substituted aromatic resonances in the (*R*)- and (*S*)-diastereomers respectively. Using these

observations it was therefore possible to determine the configuration of unknown benzhydrols by examination of the shift in the proton resonances of their aromatic groups upon derivatization with α-cyano-α-fluoro-*p*-tolylacetic acid **31** of known configuration.

Dufrasne *et al.* have reported the use of 1*R*-myrtenal **32** as a reagent for determining the enantiomeric excess for a range of α- and β-aryl amines.[47] This simple approach exploits the fact that these amine containing compounds can readily form imines with the aldehyde moiety of myrtenal (Scheme 16).

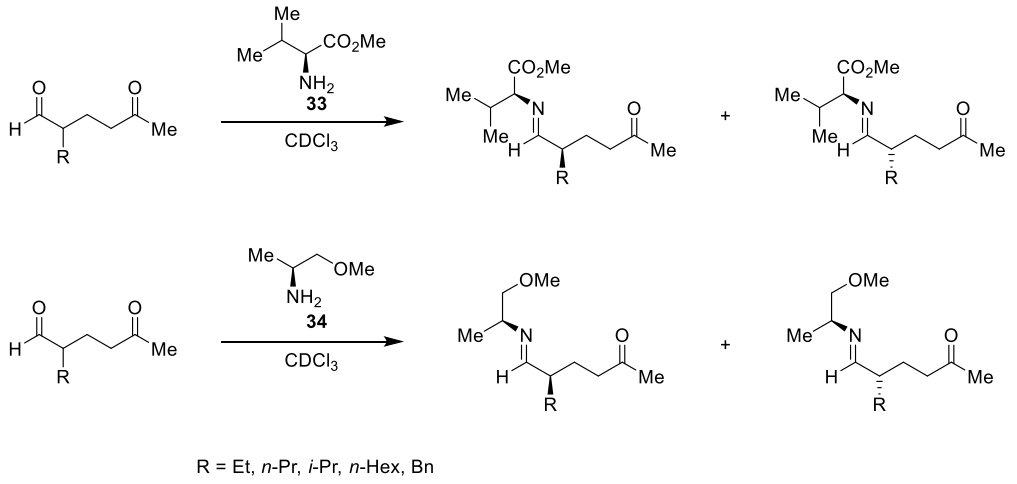


Scheme 16 - The formation of diastereomeric imines between 1*R*-myrtenal 32 and α- or β-aryl amines

It was shown that integration of the imine protons in the ^{1}H NMR spectrum of the derivatization product was particularly useful for determining the diastereomeric ratio (and thus the enantiomeric ratio of the starting amine) as their resonances were unhindered by other resonances. The determination of the enantiomeric excess of amino alcohols which do not contain aryl groups proved difficult using this method and Dufrasne has since reported that this can be overcome by using proton decoupled ^{13}C NMR spectroscopy.[48] This updated method found that resonances for both of the carbon atoms attached to the imine nitrogen could be accurately integrated to determine enantiomeric excess.

The formation of imine diastereomers was also reported by Gellman *et al.* for determination of the enantiopurity of α-substituted aldehydes synthesised in chiral pyrrolidine-catalysed Michael addition reactions.[49] By derivatization of the Michael

addition products with either amine **33** or **34** (Scheme 17), it was reported that the ^{1}H NMR spectrum of the resultant diastereomeric imines could be used to determine the enantiomeric excess of the δ-keto-aldehyde products.



Scheme 17 - Derivatization of Michael addition products with amines 33 and 34 to determine their enantiomeric excess

Gellman reported that in all cases the imine doublet resonances were able to be used to determine the enantiomeric excess of the δ-keto-aldehyde products with enantiomeric excess values obtained from both amine derivatization agents in good agreement with each other, and with values obtained from GC or HPLC analysis.

In 2006, Alexakis *et al.* reported a number of derivatization agents **35-37** (Figure 13) for determining the enantiomeric excess of chiral cyclic secondary alcohols.[50]

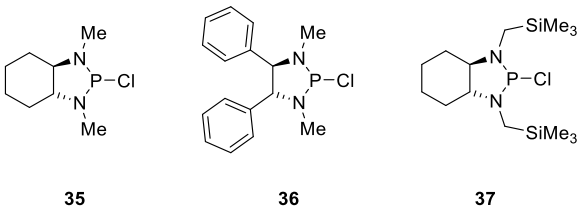
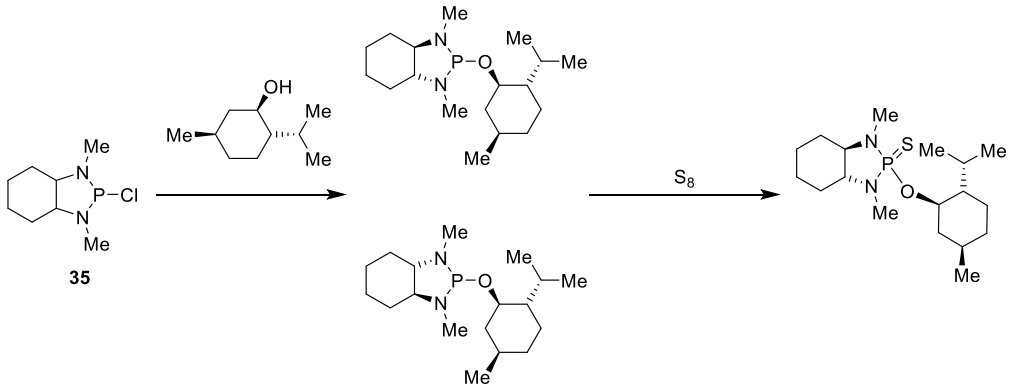


Figure 13 – Diamino-phosphorus chiral derivatization agents developed by Alexakis

Alexakis demonstrated how ^{31}P NMR spectroscopy was a useful tool to determine enantiomeric excess using diamino-phosphorus (III) compounds to form diastereomers from their reaction with cyclic secondary alcohols (Scheme 18).

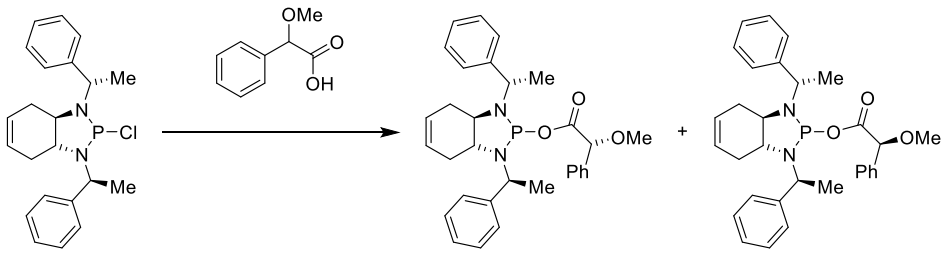


Scheme 18 – A chiral diamino-phosphorus auxiliary 35 developed for determining the enantiopurity of chiral alcohols

It was reported that reaction of a chiral cyclic secondary alcohol with derivatization agent **35** led to a pair of diastereomeric P(III) complexes *via* formation of a phosphorus oxygen bond. The ^{31}P NMR spectrum of this mixture of complexes showed distinct baseline separated resonances for the phosphorus atom in each diastereomer. These signals could be integrated, the ratio of which correlated to the enantiomeric excess of the starting alcohol. The chiral derivatization agents derived from cyclohexane-diamine were deemed the best since the rigidity of the

cyclohexane ring of their adducts produced greater chemical shift differences and their synthesis was less expensive than the diphenyl derivative. Alexakis noted that reaction of the complexes with sulphur resulted in stable P(V)=S complexes that could be purified by chromatography. In some cases, this further reaction with sulphur produced greater baseline separation in the ^{31}P NMR spectra. It was also noted that this protocol could be used to determine the absolute configuration of a chiral cyclic secondary alcohol of unknown stereochemistry. This was because alcohols with an (*S*)-configuration shifted the phosphorus resonance upfield in the ^{31}P NMR spectrum of the derivatized complex relative to the corresponding complex of its (*R*)-enantiomer.

A similar study by De Parrodi *et al.* reported how this class of chiral derivatization agent was also applicable to determining the enantiomeric excess of chiral carboxylic acids.[51] De Parrodi used a similar chiral phosphorus derivatization agent (**38**) which was reacted with chiral carboxylic acids to demonstrate that baseline separated resonances for the resultant diastereomeric mixture in the ^{31}P NMR spectrum could be accurately integrated to determine the enantiomeric excess of the parent carboxylic acid (Scheme 19).

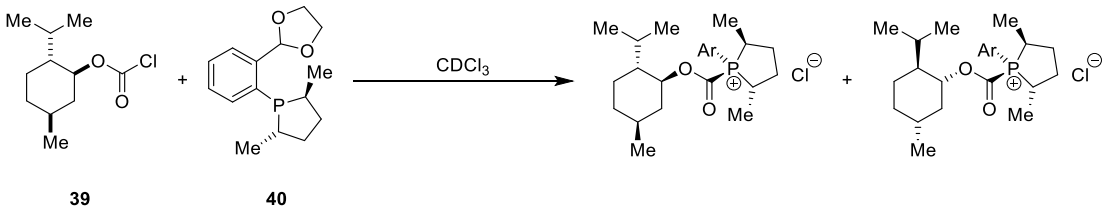


Scheme 19 – Diamino-phosphorus derivatization agent 38 for chiral carboxylic acids reported by De Parrodi

The report showed that for the case of carboxylic acids, the 4-cyclohexene-1,2-diamine derived phosphorus compound **38** provided the largest separation of

phosphorus resonances compared to similarly derived cyclohexane compounds and the derivatization agent **35** reported by Alexakis[50] for chiral cyclic secondary alcohols.

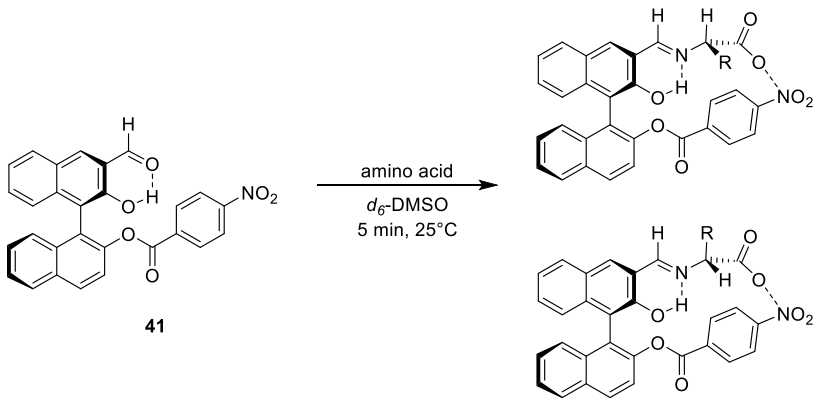
In recent years, Garner *et al.* reported the use of menthyl chloroformate **39** as a chiral derivatization agent for determining the enantiopurity of chiral tertiary phosphines.[52] The reaction of racemic menthyl chloroformate with chiral phospholane **40** produced a mixture of diastereomeric salts which were found to be distinguishable by ^{31}P NMR spectroscopy (Scheme 20).



Scheme 20 – Diastereomeric salts formed from the use of menthyl chloroformate 39 as a chiral derivatization agent for chiral phosphines

Garner demonstrated that this technique led to clean formation of the diastereomeric salts and baseline separation of a pair of phosphorous resonances associated with these diastereomers. Scalemic sampling proved that enantiomeric excesses of up to 98% could accurately be determined and that no kinetic resolution occurred upon derivatization.

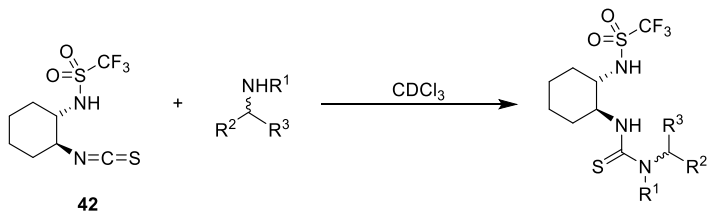
A chiral shift reagent for amino acids based on resonance-assisted hydrogen bonding was reported by Chin *et al.* in 2004.[53] BINOL based aldehyde **41** was found to form stable imines with the amine moiety of amino acids (Scheme 21) whose diastereomeric imine proton resonances were baseline resolved in the resultant ^{1}H NMR spectrum.



Scheme 21 - The use of BINOL based aldehyde 41 for determining the enantiomeric excess of chiral amino acids by formation of hydrogen bonded imines

It was reported that the ^{1}H NMR signal for the imines formed were very strongly shifted downfield to an area of the spectrum devoid of other resonances due to the resonance-assisted hydrogen bonding. This results in the integration of the diastereomeric resonances being more accurate. Computational analysis determined that the minimum structures for the diastereomeric imines had their carboxylate groups in van der Waals contact with the nitro groups. Chin demonstrated how these computational studies could be used to determine the absolute configuration of an amino acid since, for L-alanine, the imine hydrogen bond is shorter than for D-alanine and therefore stronger. This results in the imine proton resonance being shifted further downfield for the L-alanine diastereomer than the D-alanine diastereomer. This relationship was found to be consistent for other chiral amines with protons at their α-position.

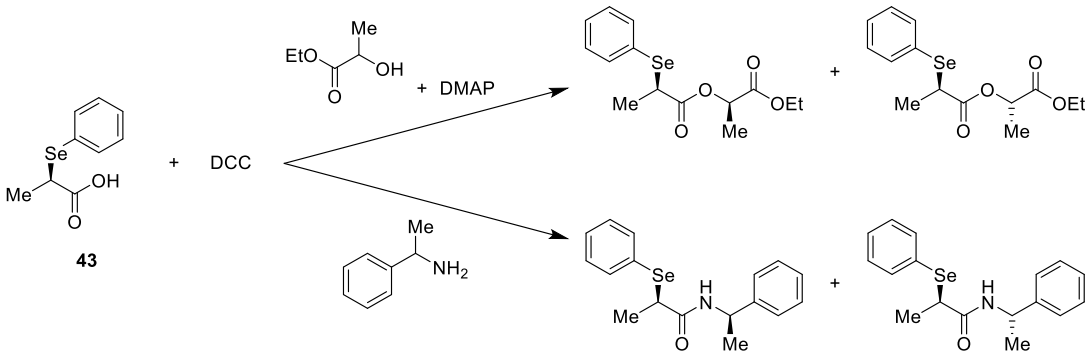
Wagner *et al.* presented the first known trifluoromethanesulfonamide-containing derivatizing agent for determining the enantiomeric excess of chiral amines and amino alcohols.[54] Derivatization agent **42** was synthesised from (1*S*,2*S*)-cyclohexane diamine and its isothiocyanate fragment reacted with a range of chiral primary and secondary amines to afford thiourea derivatives (Scheme 22).



Scheme 22 – The first chiral derivatization agent (42) to utilise a diagnostic CF_3 group

Upon derivatization with a racemic amine, two resonances were seen in the ^{19}F NMR spectrum for the diastereomeric trifluoromethyl groups of the resultant mixture of complexes. These resonances were sufficiently resolved to allow for accurate integration and further investigation with scalemic samples of chiral amine proved the technique's viability for determining the enantiomeric excess of chiral amines. It is notable that $\Delta\delta$ values were large enough to provide accurate integration, which is remarkable given the large distance (up to 8 atoms) between the diagnostic trifluoromethyl group and the chiral centre of the amine in the derivatization complex.

A few years ago, Ananikov reported a selenium-based NMR protocol which was applicable to determining the enantiomeric excess of chiral alcohols and amines.[55] ^{77}Se NMR spectroscopy was identified as an excellent tool for determining enantiomeric excess through modelling studies. (*R*)-2-phenylselenopropanoic acid **43** was prepared and reacted with a number of chiral amines and alcohols to yield well resolved diastereomeric amide and ester complexes respectively (Scheme 23).



Scheme 23 - Selenium-based NMR protocol for determining the enantiomeric excess of chiral alcohols and amines

The advantage of this approach is that the only resonances seen in the ^{77}Se NMR spectrum after derivatization are well resolved for each of the two diastereomeric complexes formed. This avoids the problems sometimes associated with using ^{1}H NMR spectroscopy whereby diagnostic resonances can overlap with other signals in the spectra. It was also noted that, in some cases, ^{1}H and ^{13}C NMR spectroscopy could be used to determine enantiomeric excess, however, ^{77}Se NMR spectroscopy provided greater signal separation ($\Delta\delta$ values up to 6 ppm) when compared to both ^{1}H and ^{13}C NMR spectroscopy.

1.2.3 Chiral Gas Chromatography

Chiral chromatographic methods are frequently used for the separation of enantiomeric compounds and for determining their enantiomeric excess. One of the most common chromatographic methods employed is chiral gas chromatography. The technique typically exploits hydrogen bonding and coordination interactions[56,57] between a chiral stationary phase and the chiral analyte to separate enantiomers, with modified cyclodextrins[58] often used as chiral stationary phases. The chiral stationary phase is formed by attachment of a chiral compound, such as a cyclodextrin (Figure 14) to the surface of an achiral stationary phase such as silica. The two enantiomers of the chiral substrate to be separated are vaporised and passed through the column as the mobile phase and will interact differently with the chiral stationary phase based on their affinity towards it. The two enantiomers will thus be

retained on the column for different amounts of time and become separated from the mixture. This method can be advantageous over other chromatographic methods such as HPLC because it is very fast, efficient and highly sensitive. However, the principle disadvantage of this technique is that it can only be used to analyse compounds that are volatile and thermally stable. The high temperatures at which the separations are carried out can also reduce the lifetime of the chiral stationary phases used as they can thermally degrade or racemise.[59]

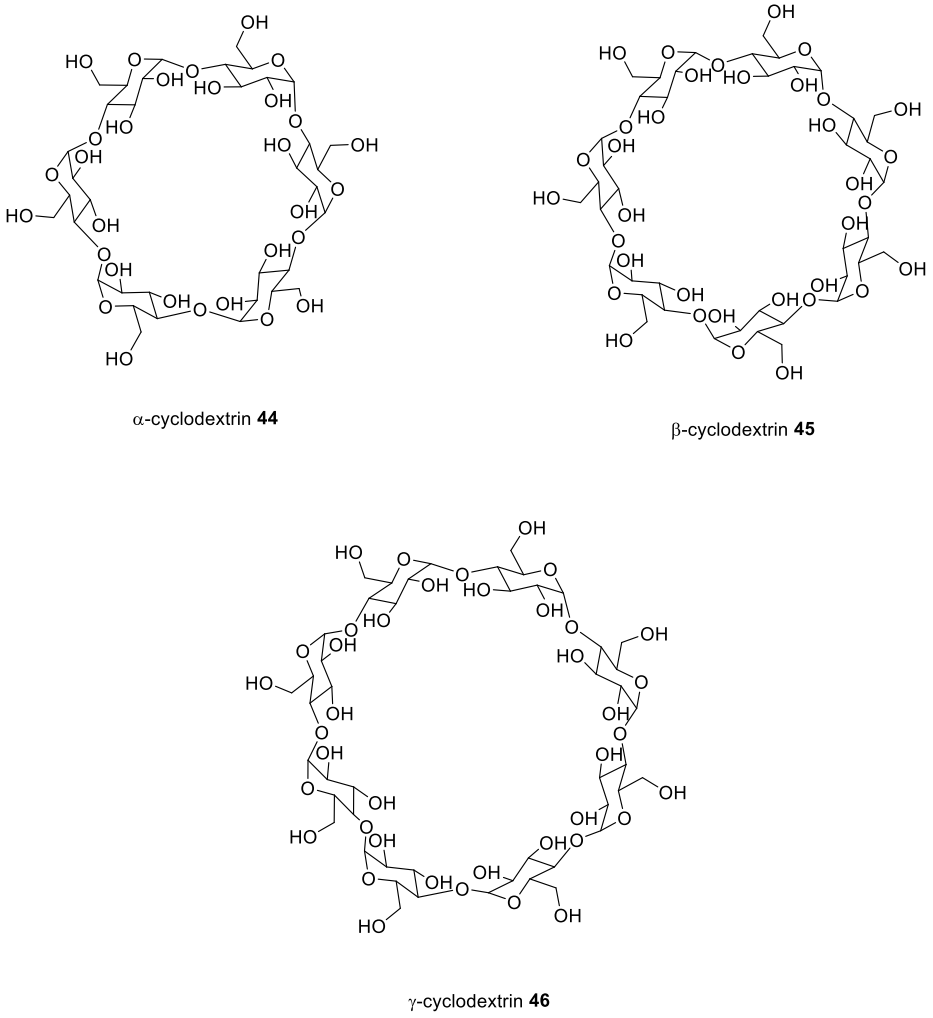
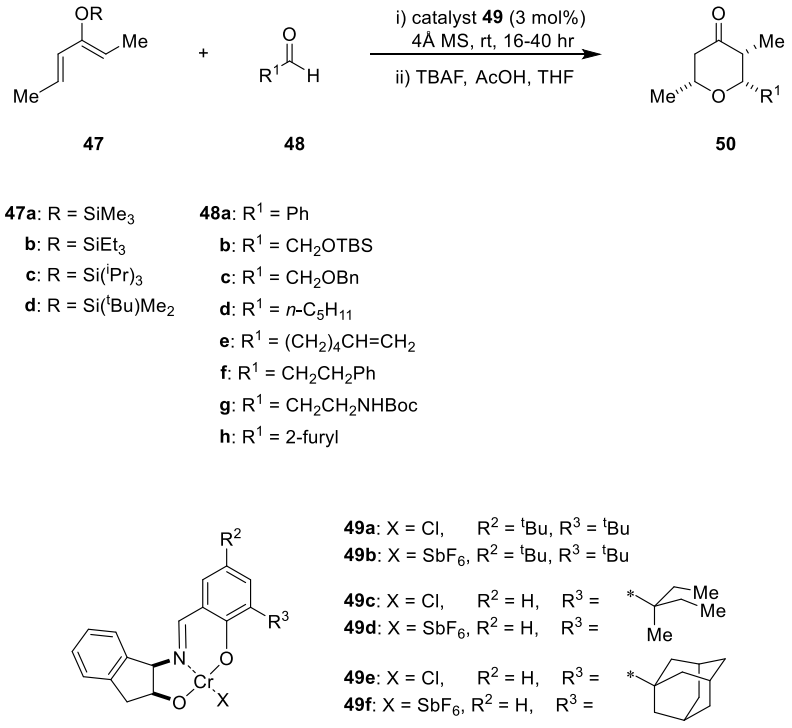


Figure 14 - Structures of typical chiral gas chromatography stationary phases, α-cyclodextrin 44, β-cyclodextrin 45 and γ-cyclodextrin 46

In 1977, Frank *et al.* published the separation of amino acid enantiomers using a chiral polysiloxane stationary phase which was found to be thermally stable at the separation temperature of 175 °C.[60]

In 1999, Jacobsen *et al*. reported the determination of the enantiomeric excess of a range of hetero-Diels-Alder products using chiral gas chromatography.[61] Jacobsen reported the use of chiral tridentate chromium(III) catalysts to catalyse the reaction between *O*-silyl-protected hexadienes **47a-d** and a range of aldehydes **48a-h** to afford substituted tetrahydropyranones **50a-h** after silyl deprotection (Scheme 24).



Scheme 24 - Chromium(III) catalysed enantioselective hetero-Diels-Alder reactions between hexadienes 47a-d and aldehydes 48a-h to afford chiral substituted tetrahydropyranones 50a-h

Jacobsen reported excellent diastereoselectivity and enantioselectivity for these chromium(III) catalysed hetero-Diels-Alder reactions, particularly those catalysed by **49f**, and was able to determine the enantiomeric excesses of the tetrahydropyranone products using chiral gas chromatography. Jacobsen employed a

β-cyclodextrin **45** chiral stationary phase operating between 110 °C and 165 °C to provide good separation for the tetrahydropyranone enantiomers.

Reetz *et al.* have reported a method for high throughput screening of chiral catalysts for optimising acylation based kinetic resolution reactions of racemic 2-phenyl-1-propanol catalysed by mutant lipases.[62] This method uses a configuration of two columns and injectors in one oven so that two samples can be analysed in tandem. However, for this method to be truly effective multiple columns and detectors would be required to be coupled together, so that large numbers of samples could be run continuously, which would obviously incur large costs.

1.2.4 Chiral HPLC

High performance liquid chromatography is a technique used to separate compounds in a mixture by pumping them in a mobile phase at high pressure over a stationary phase. The components are separated due to their differing interactions with the stationary phase; these interactions can be based on molecular size and ionic or polar interactions. In order to be applied to the separation of chiral components a chiral stationary phase must be used. Typically, a chiral molecule is coated onto a stationary phase such as silica and it is the differing diastereomeric interactions between the chiral components and the chiral stationary phase that determines the retention time of each of the chiral components.

The advantage of this technique is that it can be automated once an appropriate chiral stationary phase and solvent system have been identified. However, the pre-packed columns required for the technique are very costly, cannot handle crude reaction mixtures as they are often irreversibly modified by reaction impurities, and their separation power deteriorates over time. There is also no universal chiral stationary phase to separate all chiral compounds, which leads to significant development costs associated with determining the appropriate column/conditions required to separate the enantiomers of a target chiral compound. There are also sustainability issues arising due to the relatively large amount of solvents used by this chromatographic technique. In order to use this technique for the quick or constant analysis of a large number of samples, arising from a catalyst screening, it

is often necessary to screen a number of columns and detectors before a suitable system is determined. This screening process can therefore have significant cost implications which need to be evaluated to determine whether chiral HPLC is an appropriate technique to determine enantiomeric excess.[63]

Nevertheless, this approach has proven to be very popular, primarily due to its ability to be automated. For example, in 1998 Olsen *et al.* reported a chiral HPLC method for determining the enantiomeric excess of the selective serotonin reuptake inhibitor, fluoxetine hydrochloride **51**,[64] using a chiral stationary phase comprised of cellulose tris-(3,5-dimethylphenyl carbamate) coated silica (Figure 15).

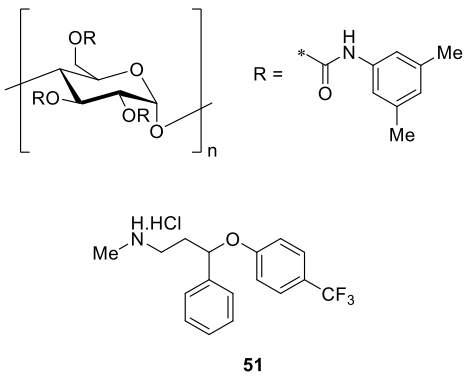
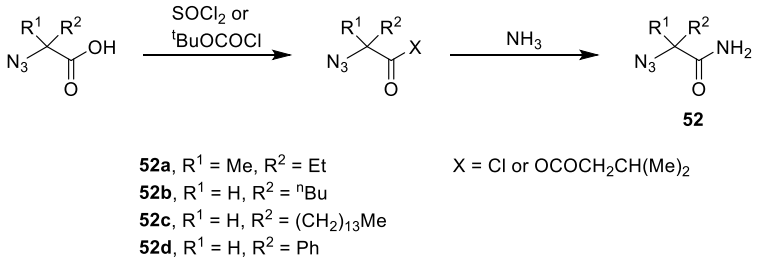


Figure 15 – Cellulose based chiral stationary phase - Chiralcel OD-H and the structure of (*rac*)-fluoxetine hydrochloride 51 below

Olsen reported that, separation of the enantiomers of fluoxetine on the chiral stationary phase was highly sensitive towards the presence of isopropyl alcohol used in the mobile phase at room temperature, and determined that peak separation could be improved greatly by cooling the column down to 1 °C.

Meldal *et al.* have reported methodology for the preparation of a number of racemic α-azido acid amides (Scheme 25) followed by separation of their enantiomers by HPLC.[65]



Scheme 25 – Meldal's synthesis of α-azido acid amides 52

By using the antibiotic teicoplanin A_2 immobilised onto silica gel, it was shown that these racemic α-azido acid amides could be separated cleanly since the immobilised teicoplanin fragments bind to the D- enantiomers more strongly than their L-counterparts. Teicoplanin A_2 is a mixture of components, each of which contains a different side amide chain R. The five major components of teicoplanin A_2 are shown in Figure 16. This resulted in the L-form being eluted more quickly than the D-form. Clean separation was reported for amides **52b-d**, however, the α-methyl amide **52a** could not be separated by the teicoplanin column, due to the relative similarity in size of its methyl and ethyl R groups.

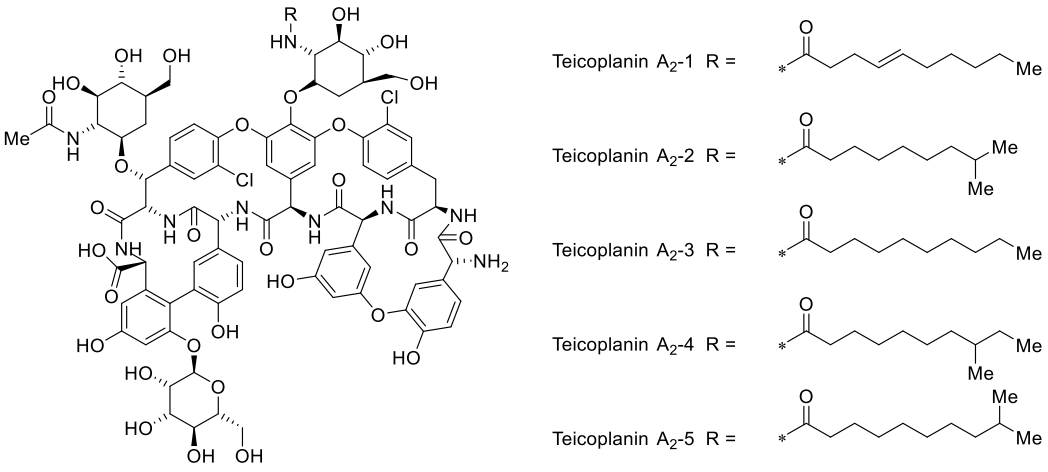
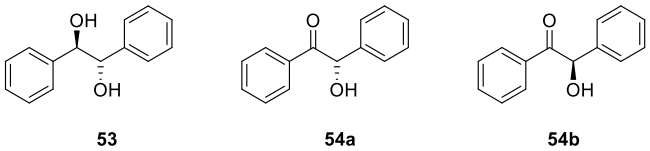


Figure 16 - Structure of the five major components of teicoplanin

In a typical screening approach, Welch *et al.* demonstrated high-throughput HPLC analysis for determining the enantiopurity and concentration of (*R*,*S*)-hydrobenzoin present in a mixture of (*R*,*S*)-hydrobenzoin **53**, (*R*)-benzoin **54a** and (*S*)-benzoin **54b** (Figure 17).[66]



53 **54a** **54b**

Figure 17 - Structures of (*R*,*S*)-dihydrobenzoin 53, (*S*)-benzoin 54a and (*R*)-benzoin 54b

This chiral HPLC protocol was used to screen a range of chiral catalysts for the stereoselective reduction of benzoin **54** to (*R*,*S*)-hydrobenzoin **53**. It's use enabled the enantiomeric excess of mixtures of varying amounts of (*R*,*S*)-dihydrobenzoin, (*R*)-benzoin and (*S*)-benzoin present in a 96-well plate format to be determined by HPLC analysis using an amylose tris-(3,5-dimethylphenyl carbamate) coated silica chiral stationary phase (Figure 18).

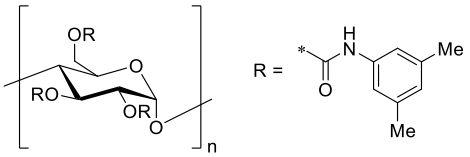


Figure 18 – Amylose based chiral stationary phase - Chiralpak AD-H

This chiral stationary phase was able to cleanly separate the three components of the mixture in under six minutes per sample with the enantiomeric excess of the benzoin determined to within 2% of known enantiomeric excess values. This work

demonstrates how chiral HPLC analysis can be used as an accurate and quick procedure for catalyst screening for the asymmetric reduction of benzoin to (*R*,*S*)-dihydrobenzoin. It was noted that using multi-parallel HPLC analysis enabled 96-well plate analysis of chiral samples in as little as 1.5 hours.

1.2.5 Polarimetry and Circular Dichroism

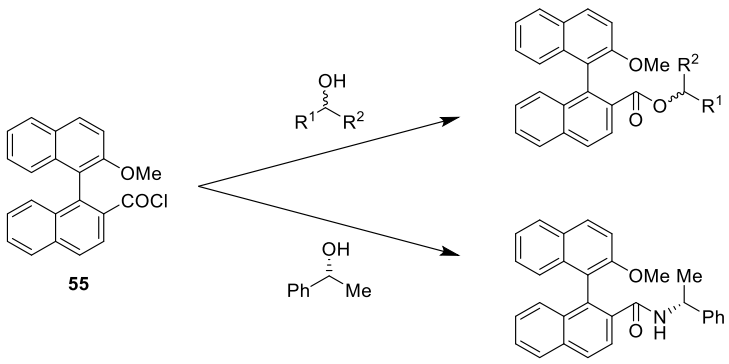
An important property of enantiomers is that they rotate plane polarised light to an equal degree in opposite directions. Polarimetry uses a polarimeter to measure the optical rotation of a solution of chiral material in a specific solvent at a known temperature and concentration. To measure the optical rotation the polarimeter shines monochromatic light of a given wavelength through a plane-polarizing filter and through the chiral solution onto a detector which measures the rotation of the plane polarized light due to its interaction with the chiral solution. A chiral solution will rotate the light to a degree related to the enantiomeric excess of the solution with the absolute configuration determined by the sign of the rotation. A racemic solution will produce a net rotation of zero, since equal amounts of each enantiomer will rotate the plane polarized light equally, but in opposite directions. The specific rotation value obtained can be compared with a known value for an enantiomerically pure sample of a chiral compound, as long as it is measured at the same concentration, solvent and temperature. Furthermore, the sign of rotation can also be used to assign the configuration of the chiral compound.

However, polarimetry is now less well used to determine enantiomeric excess since more accurate methods have been developed, and it is primarily used to just determine absolute configuration from the sign of the rotation of the plane polarized light. The method does still have the advantage that it requires no chemical reactions or derivatization before taking the measurement. However, it has the disadvantage that contamination from chiral impurities can severely affect the specific rotation obtained, with the relationship between the value of the optical rotation and enantiomeric excess not always linear.

Although polarimetry is now disfavoured as a method of determining enantiomeric excess, another optical method, circular dichroism is becoming increasingly

popular. Circular dichroism measures the differential absorption of left and right polarized light by a chiral medium. Equal amounts of left and right circularly polarized light are alternately radiated into the sample, a chiral sample absorbs the two polarizations by differing amounts and the measurement of this difference across a range of wavelengths is used to produce the CD spectrum. The characteristic change in the CD curve in the region of the absorption band of a chiral compound is known as a Cotton effect and the absorbance maximum of this effect is used to determine the enantiomeric excess by comparison with a sample that is known to be enantiomerically pure. Enantiomers have identically opposite CD spectra as they interact in equally opposite amounts with the left and right circularly polarized light that the sample is irradiated with. Whilst circular dichroism is an accurate technique that doesn't require any chiral derivatization before analysis, it often requires complexation of the chiral compound to a chromophore when the chiral molecule being analysed does not contain one within its structure.

In 2001, Hattori *et al.* developed the method of using a racemic derivatization agent for measuring enantiomeric excess by circular dichroism spectroscopy.[67] Chiral alcohols and amines were derivatized using binaphthyl derivatizing agent **55** (Scheme 26).



Scheme 26 – Hattori's derivatization approach for determining enantiomeric excess by CD spectroscopy

The binaphthyl derivatization agent chosen by Hattori has a strong CD signal and it was shown that the CD spectrum of the diastereomeric ester or amide products formed was influenced by the enantiopurity of the respective alcohol or amine component. Thus, a discernible difference between the CD spectra of the diastereomers formed between reaction of racemic **55** and an alcohol was observed. Scalemic sampling showed that the value of $\Delta\varepsilon$ at 234 nm changed linearly with respect to the enantiomeric excess of the alcohol. After prior calibration with a sample of known 100% enantiomeric excess it was reported that enantiomeric excess could be determined with an accuracy of ±5%.

Anslyn *et al.* have published a method for determining the enantiomeric excess of chiral carboxylic acids using circular dichroism.[68] The reported method involves formation of a copper (II) complex **56** with a chiral carboxylic acid (Figure 19).

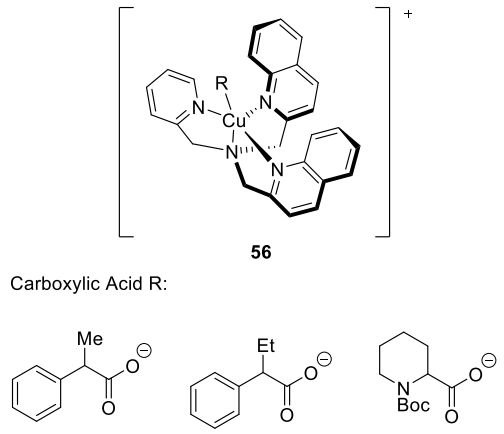
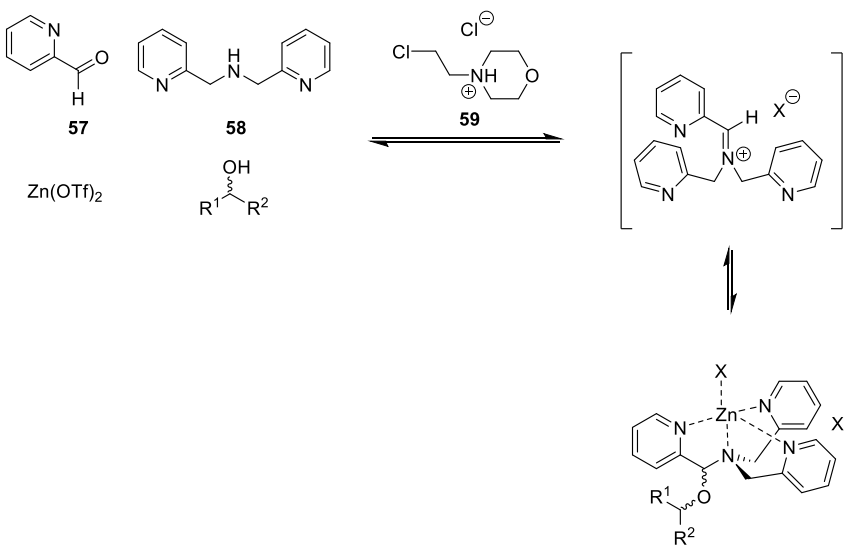


Figure 19 - Copper complex 56 of carboxylic acids whose enantiomeric excess are determined by CD spectroscopy

Anslyn reported that addition of a chiral carboxylic acid to copper complex **56** resulted in strong signals being observed in the resultant CD spectrum. The absorption of the first Cotton effect in the CD spectra was positive when the (*S*)-carboxylic acid was used and negative when the (*R*)-enantiomer was employed, with a λ_{max} observed at 238 nm. This is due to formation of chiral copper propeller

compounds. For the case of (*S*)-2-phenylbutyric acid an *M* propeller complex was formed, whilst for (*R*)-2-phenylbutyric acid, a *P* propeller was produced. Since the (*S*)- and (*R*)-complex spectra are equal and opposite to each other, a calibration curve was produced from which it was determined that enantiomeric excess changed linearly at an absorption value at 238 nm, with a maximum positive absorption observed for the enantiopure (*S*)-enantiomer, and a maximum negative absorption observed for the enantiopure (*R*)-enantiomer. The method reported was able to determine enantiomeric excess to within 4% of the true value, with lower errors seen for carboxylic acids that produced the largest amplitudes in the CD spectra.

In 2012 Anslyn *et al.* produced another circular dichroism method for determining the enantiomeric excess of chiral secondary alcohols.[69] Diastereomeric zinc complexes were formed from pyridine-2-carboxaldehyde **57**, *bis*-(2-pyridylmethyl)amine **58**, zinc triflate and a chiral secondary alcohol, using 4-(2-chloroethyl)morpholine hydrochloride **59** as a catalyst (Scheme 27).



Scheme 27 - Synthesis of propeller-like zinc complexes by Anslyn

It was reported that the CD spectra for the zinc complexes formed correlated to the chirality of the alcohol used, with all (*S*)-alcohols investigated producing a positive

Cotton effect, with their corresponding (*R*)-enantiomers giving mirrored negative Cotton effects. Scalemic sampling using three chiral alcohols (Figure 20) was used to produce calibration curves which showed a linear relationship between ellipticity (measured at the λ_{max} of the first Cotton effect) and enantiomeric excess. Samples of unknown enantiomeric excess were employed to determine the validity of Anslyn's method, and it was noted that enantiomeric excess could be determined to within 3% of their true value.

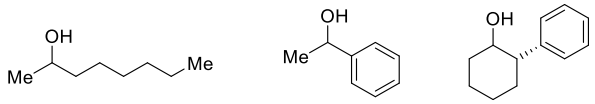
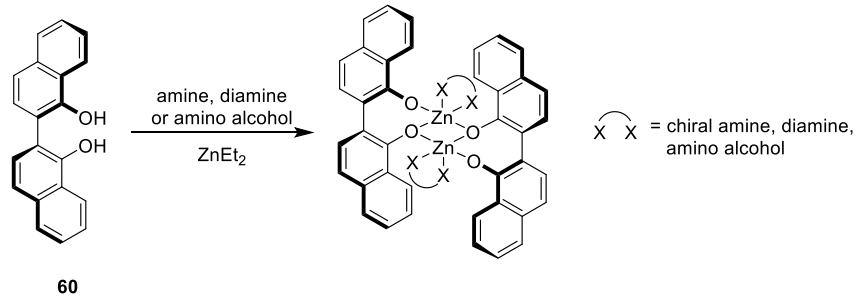


Figure 20 – Chiral alcohols investigated using Anslyn's propeller system

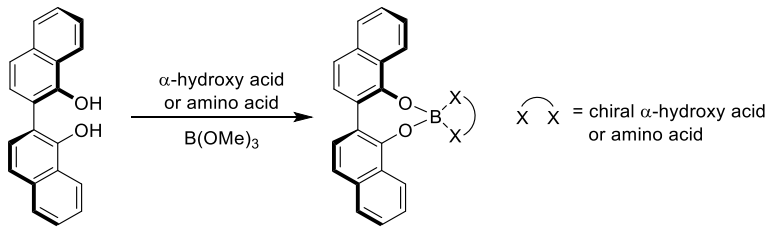
More recently, Wolf *et al.* published a versatile protocol for determining the enantiomeric excess of chiral amines, diamines, amino acids, amino alcohols and α-hydroxy acids.[70] These substrates were reacted with binaphthol **60** and diethylzinc to yield dimer complexes (Scheme 28) which exhibited strong Cotton effects at 350 nm.



60

Scheme 28 – The formation of zinc dimers for determining the enantiomeric excess of chiral amines, diamines and amino alcohols by CD spectroscopy

Upon inspection of the CD spectra of these zinc complexes, Wolf noted that the sign of the maximum CD amplitude related to the absolute configuration of the substrate. Amino alcohols with a single (*R*) stereocentre gave a positive CD response at 350 nm, whilst (*S*) enantiomers gave a negative signal. Conversely, amines with an (*R*) configuration gave a negative CD response and for (*S*) configured amines a positive CD maximum was observed. It was observed that enantiomeric excess related to the chiroptical response in a non-linear manner, however, calibration enabled enantiomeric excess to be determined for samples of diamines and amino alcohols of unknown *e.e.* to within 3% of their true values. For the cases of α-hydroxy acids and amino acids, Wolf employed a boron based approach, substituting trimethylborate for the diethylzinc to yield four-coordinate borate complexes (Scheme 29).

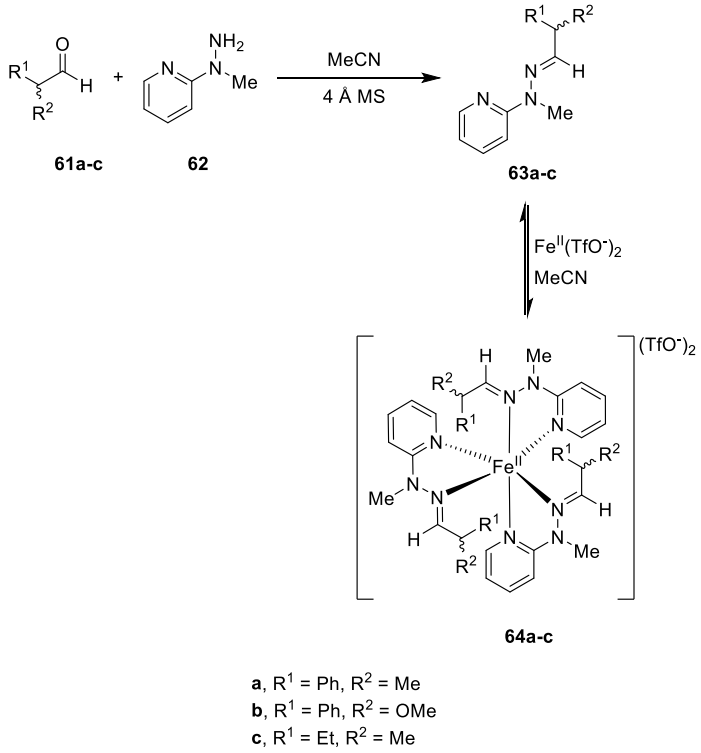


60

Scheme 29 – A boron based CD sensor for use with α–hydroxy acids and amino acids

As with the zinc based complexes Wolf reported that it was possible to discern the configuration of amino acid and α-hydroxy acid substrates, however, he did not report the use of this method to determine enantiomeric excess. In both of Wolf's reported systems the configuration of the binaphthol **60** is induced by its complexation to the zinc or boron atom, since the starting binaphthol **60** has no inherent stereochemistry due to free rotation about the bond connecting the two ring systems. Derivatization with a chiral substrate then creates diastereomeric complexes that are sufficiently different in energy to enable their ratio to be analysed by circular dichroism.

In 2014, by combination of their protocols for chiral primary amines[71,72] and ketones,[73] Anslyn *et al.* have developed a method for determining the enantiomeric excess of α-chiral aldehydes **61a-c** using circular dichroism spectroscopy.[74] The aldehydes were converted to hydrazones **63a-c** by condensation with 2-(1-methylhydrazine)pyridine **62** in acetonitrile and then mixed with iron triflate to form six-coordinate metal complexes **64a-c** which were CD active (Scheme 30).



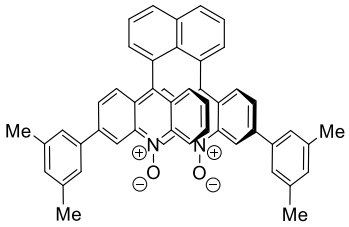
Scheme 30 – Anslyn's reported protocol for determining the enantiopurity of chiral aldehydes 61a-c

These hydrazones were formed exclusively as their *E*-isomers due to disfavoured interactions between the R groups and the *N*-methyl moiety. A large CD response was seen for the octahedral iron complexes formed from chiral aldehydes **61a-c** between 334 and 345 nm. Calibration curves were generated for the individual complexes using three control samples of known enantiomeric excess, confirming a linear relationship between enantiomeric excess and the measured molar ellipticity.

Anslyn noted that this method could be used to determine the enantiomeric excess of α-chiral aldehydes to within 5% for all the aldehydes analysed, and that this protocol was an excellent method for high throughput analysis, since the derivatization process from initial imine formation, through complexation, to CD analysis of 96 samples could be achieved in around one hour.

1.2.6 Ultraviolet-visible and Fluorescence Spectroscopy

Other spectroscopic techniques have also been employed to determine enantiomeric excess with Wolf *et al.* demonstrating that UV-vis spectroscopy could be used to determine the enantiopurity of amino acids, amines, amino alcohols and carboxylic acids in aqueous solution.[75] Wolf reported how chiral substrates could competitively bind to Sc[*N*,*N*'-dioxide **65**]$_2$ (Figure 21) displacing the *N*,*N*'-dioxide **65** ligand and causing a reduction of the charge transfer band associated with the scandium complex.



65

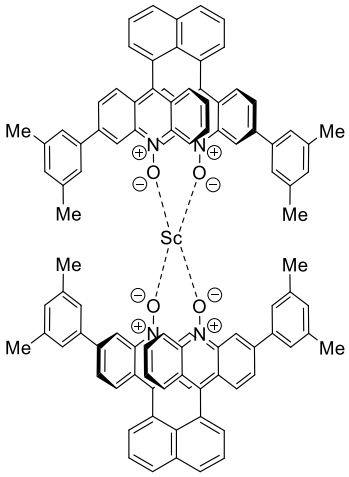
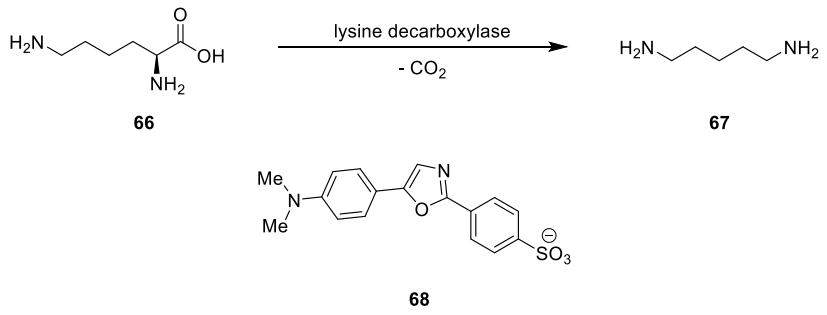


Figure 21 - The structures of *N*,*N*'-dioxide 65 ligand and Sc[*N*,*N*'-dioxide 65]$_2$ complex

Since the Sc(III) complexes of amino acids, amines, amino alcohols and carboxylic acids exhibit no UV absorption above 350 nm then any absorption measured relates to the Sc[*N*,*N*'-dioxide **65**]$_2$ complex. The competitive binding was found to be stereoselective since (*S*)-valine was more effective in replacing the *N*,*N*'-dioxide **65** from the metal centre of the Sc[(+)-**65**]$_2$ complex. Thus, a calibration curve for enantiomeric excess vs absorption could be fitted by titration of enantiopure Sc[*N*,*N*'-dioxide **65**]$_2$ complexes with each chiral substrate. Scalemic sampling showed good agreement between the values obtained using the calibration curves and the known enantiomeric excess for valine, camphanic acid, α-cyclohexylethylamine and threoninol. Wolf noted that this method may be preferable to other protocols for enantiopurity determination due to it avoiding substrate derivatization, and its dependence on highly sensitive changes in UV-vis absorptions.

In 2008, Bailey *et al.* reported a fluorescence dye displacement based protocol for determining the enantiomeric excess of D-amino acids.[76] Bailey observed that the decarboxylation of L-lysine **66** to cadaverine **67** by lysine decarboxylase led to a measurable decrease in fluorescence. Dapoxyl **68** was used as a fluorescent dye which displays 200 times more fluorescence when complexed to the macrocycle cucurbituril, than when uncomplexed. Cadaverine is able to compete with Dapoxyl for complexation with the cucurbituril and therefore the presence of cadaverine causes a release of Dapoxyl from the complex, and thus a decrease in fluorescence (Scheme 31).



Scheme 31 - Conversion of L-lysine 66 to cadaverine 67 by lysine decarboxylase causes displacement of Dapoxyl 68 from its cucurbituril complex

Since lysine decarboxylase is enantiospecific for the L-form of lysine it is possible to relate the amount of reduction in fluorescence to the amount of L-lysine present in a scalemic sample of lysine. This relationship can be seen in Figure 22 which reveals that the rate of fluorescence decrease is linearly dependent on concentration of L-lysine in the sample. Scalemic sampling was able to show how this method was applicable to determining a broad range of enantiopurities, enabling enantiomeric excess of D-lysine to be measured as high as 99.98%, by detecting the small reduction in fluorescence of the sample due to the presence of 0.02% L-lysine (Figure 22C).

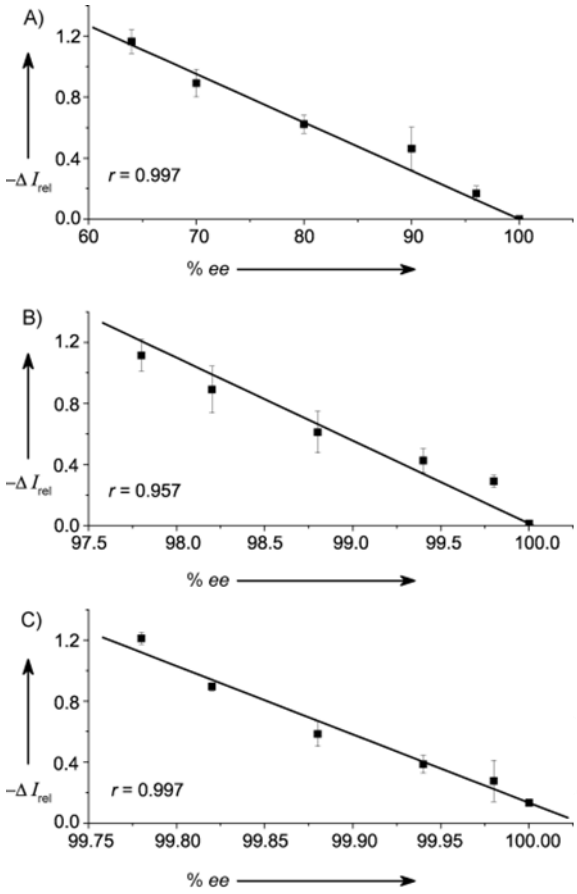
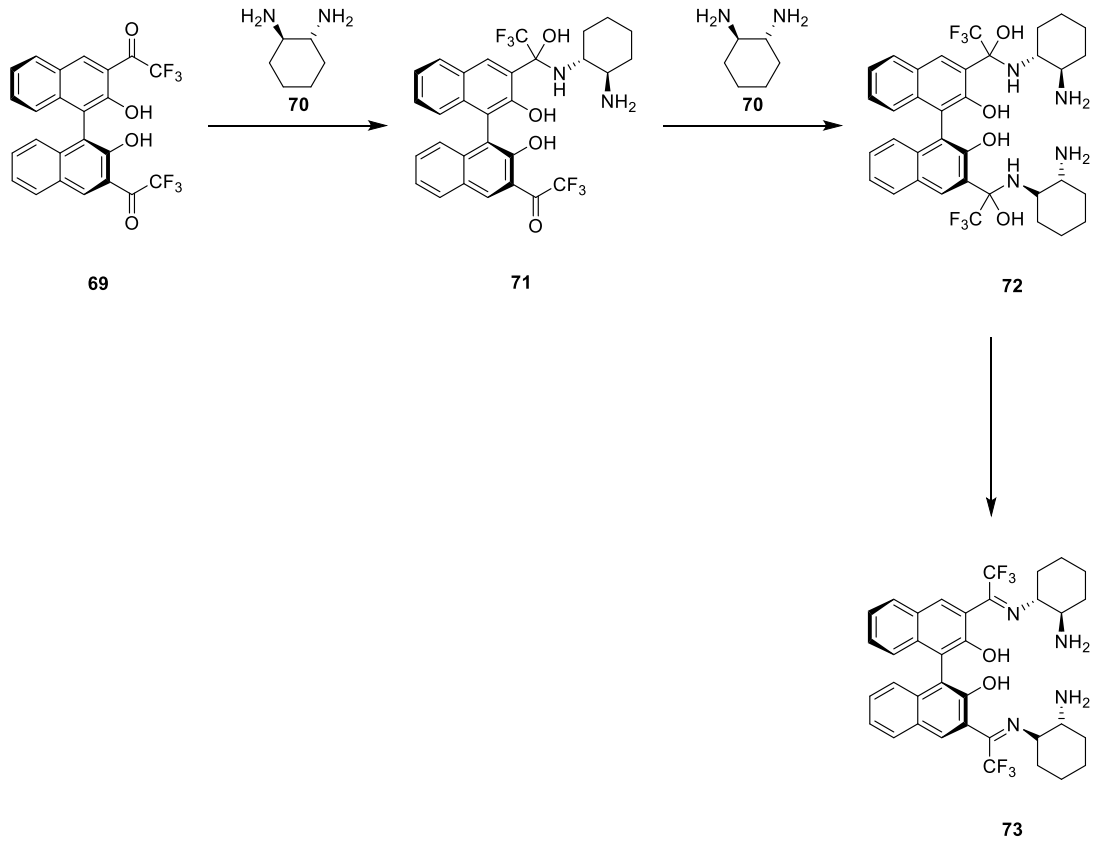


Figure 22 - Linear relationship between the *e.e.* of D-lysine and the reaction rate, shown for three ranges of enantiomeric excess

Pu *et al.* have also reported a fluorescent sensor which is able to determine the enantiomeric excess of chiral diamines.[77] Pu found that whilst (*S*)-trifluoromethyl ketone based BINOL **69** exhibits no fluorescence emission, upon addition of enantiopure (*R*,*R*)-1,2-diaminocyclohexane **70** two emissions were seen, the first emission at 370 nm and a second emission at 438 nm. Upon treatment of **69** with the (*S*,*S*)-enantiomer of the amine the same emission was seen at 370 nm, however, the emission at 438 nm was much smaller showing that the sensor displayed high enantioselectivity towards the chiral diamine. The measured fluorescence emissions were attributed to the formation of stable carbinolamine products **71** and **72** which are subsequently converted to *bis*-imine **73** over time (Scheme 32).



Scheme 32 - Reaction of trifluoromethyl ketone BINOL derivative 69 with diamine 70 to yield fluorescent hemiaminal products 71 and 72

The accuracy of this fluorescent sensor method was evaluated by analysis of scalemic samples of known enantiomeric excess of chiral diamine **70**. This method was shown to be very accurate for high values of enantiomeric excess (1-4% accuracy), however, it was found that as enantiomeric excess decreased then the accuracy of this method diminished.

In summary, the ability to discern the chirality of a compound or determine its enantiomeric excess is of great importance to modern science. This requirement is exemplified by the number of different protocols that have been developed to date, with new, more efficient methods still being developed for determining the enantiomeric excess of different types of chiral compound. In this respect it is important for chemists to determine which technique is most efficient for their particular need. For example, it is not uncommon to have to screen a number of different chiral HPLC columns before satisfactory conditions are identified to resolve the enantiomers of a target chiral analyte. Furthermore, it is often necessary to investigate a number of different solvent systems before a clean separation of enantiomers is achieved to enable the enantiomeric excess of a chiral product to be determined. A chiral HPLC system taking 20 minutes to achieve separation and running at 1 mL/min of solvent uses 20 mL of solvent per enantiomeric excess determination. By comparison, a chiral derivatization NMR spectroscopic protocol needs only 0.3 mL of deuterated solvent per experiment. Thus for a small scale laboratory, interested in optimising the sustainability of their research program, a chiral derivatization protocol may be a more desirable method of enantiomeric excess determination than the use of chiral HPLC.

2 A Simple Protocol for NMR Analysis of the Enantiomeric Purity of α-Arylglycines

Most of the joint research published by the Bull-James group involves the development of new synthetic protocols and analytical methods constructed around the chemistry of boron. Simple protocols for determining enantiomeric excess by NMR spectroscopy are of great interest to the group and previous publications have demonstrated how boronic acids can be used as templates for determining the enantiomeric excess of chiral molecules.

2.1 Introduction

The work described in the subsequent chapters of this thesis is based on the use of boronic acids as templates to develop new chiral derivatization methods. The bonding of boron is governed by a number of factors. With a ground state configuration of $1s^2\ 2s^2\ 2p^1$ the three valence electrons have little shielding from the nucleus and therefore have high ionization energies. The bonding of boron is chemically similar to carbon and can form covalently bonded networks, its electronegativity is also similar to carbon but slightly more electropositive and thus when forming covalent bonds the boron centre is left electron deficient. This bonding character means the boron atom is sp^2 hybridised in simple organoboron compounds and therefore trigonal planar, with an R-B-R bonding angle of 120° (Figure 23). Boron also has an empty 2*p* orbital which sits perpendicular to the plane of the B-R bonds that is not involved in bonding.

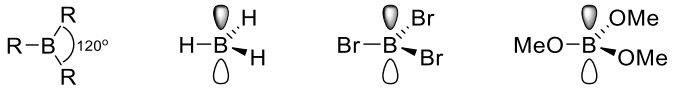
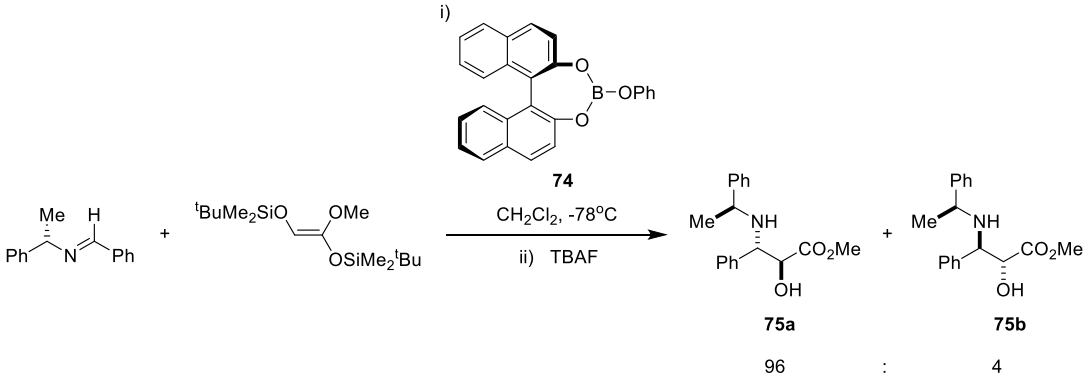


Figure 23 - The bonding in simple organoboron compounds

Boron's vacant 2*p* orbital readily interacts with electron rich species and results in boron compounds often acting as Lewis acids. These compounds can react with Lewis bases to form neutral donor-acceptor complexes that change the hybridisation of the boron to an sp^3 tetrahedron. This donation into the empty 2*p* orbital and the resultant change in shape is crucial to a lot of the chemistry and mechanisms involving the boron centre.

Organoboron reagents have long been noted for their effectiveness in synthetic reaction routes with research by Brown and Krishnamurthy earning them a Nobel Prize in 1979.[78] Donor-acceptor complexes containing N-B interactions are also well known[79,80] with the first example being reported in 1862 by Frankland, where evidence for a H_3N-BMe_3 donor-acceptor complex was reported.[81]

Yamamoto *et al.* demonstrated the usefulness of this type of interaction for the stereoselective formation of β-amino esters from the stereoselective condensation of an imine and a silyl ketene acetal (Scheme 33).[82]



Scheme 33 - Diastereoselective synthesis of β-amino ester 75

It was reported that use of the chiral boronate ester **74** resulted in diastereoselective formation of β-amino ester product **75** in 92% diastereomeric excess (*d.e*). This can be rationalised as nucleophilic attack occurring preferentially at the *Re* face of the

imine due to prior formation of an N-B complex with the imine substrate which blocks approach of the nucleophilic enolate species at the *Si* face (Figure 24).

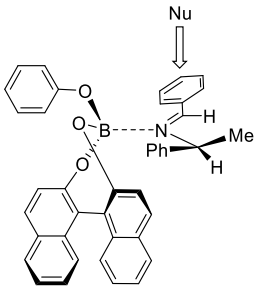
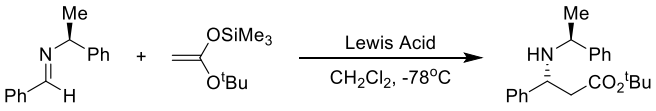


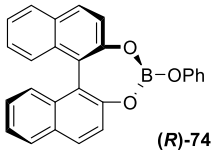
Figure 24 - Stereoselective nucleophilic attack at the *Re* face of an imine

Boronate ester **74** was also shown to be an effective catalyst for asymmetric *aza*-Diels-Alder reactions.[83,84] Having developed this methodology Yamamoto *et al.* went on to investigate the design of various iminoboronate complexes, reporting their ability to direct good diastereofacial control for both *aza*-Diels-Alder and Mannich reactions.[85] It was found that certain boronic acid complexes had the ability to sterically hinder one face from nucleophilic attack at an N-B iminoboronate complex, resulting in the generation of a new chiral centre with high enantiocontrol (Table 1). A significant advantage of such complexes reported by Yamamoto is their ability to form crystalline substrates and this property resulted in air stable compounds that improved their ease of handling during synthesis.

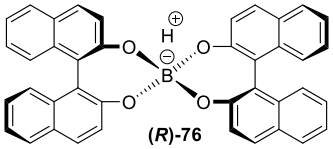
Table 1 - Effect of boronic ester on diastereomeric excess of β-amino ester formation



Lewis Acid	Yield	*d.e.* (*R*)
(*R*)-**74**	59	92
(*S*)-**74**	56	74
(*R*)-**76**	63	94
(*S*)-**76**	18	66
$B(OPh)_3$	67	78

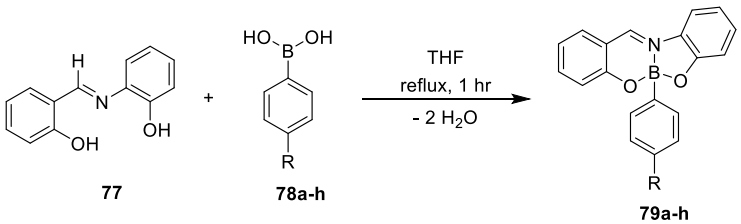


(*R*)-**74**



(*R*)-**76**

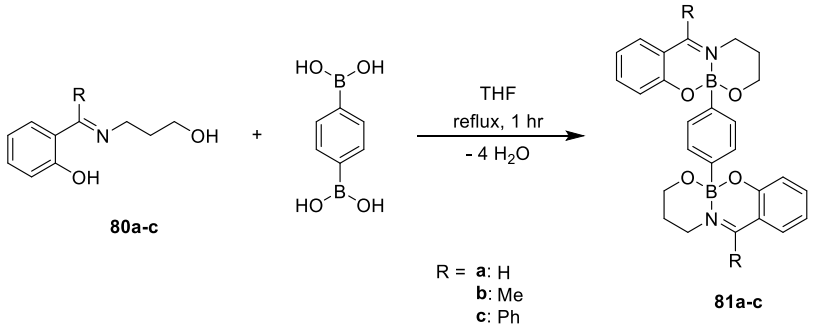
The formation of iminoboronate complexes has also attracted the interest of macrocyclic chemists.[86] In 2005, Barba *et al.* reported their route to a number of substituted iminoboronate compounds.[87] This approach utilised imine based diol **77** and phenylboronic acid template **78** to afford stable cyclised iminoboronate structures **79a-h** (Scheme 34).



R = **a**: F **e**: OMe
b: Cl **f**: CHO
c: Br **g**: COMe
d: Me **h**: CF_3

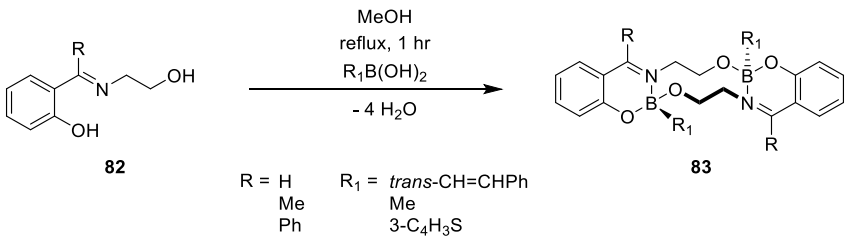
Scheme 34 - Formation of monomeric iminoboronate complexes 79a-h

Reactions for the formation of iminoboronate complexes **79a-h** returned relatively high yields with the N-B interaction confirmed from their x-ray crystal structures. These monomeric iminoboronates were then utilised in a new stereoselective route to 3,4-dihydroquinolines.[88] This success prompted the synthesis of the dimeric iminoboronate analogue where benzene-1,4-diboronic acid was used instead of the phenyl boronic acid derivatives, which reacts with two molecules of the imine.[87] Once again, this reaction afforded high yields for the synthesis of a small range of dimeric iminoboronate complexes **81a-c** derived from aliphatic imine diols **80a-c** (Scheme 35).



Scheme 35 - Synthesis of dimeric iminoboronate complexes 81a-c

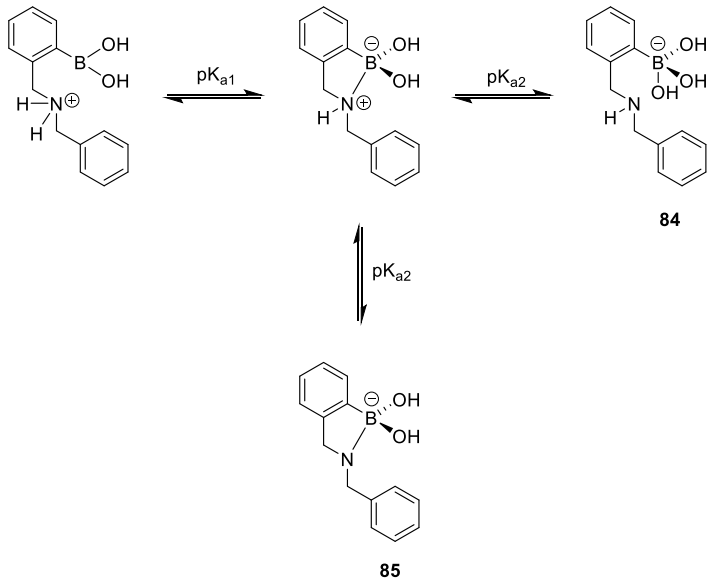
Barba *et al.* reported that variation of the length of the aliphatic chain in imine diol **80** to a two-carbon chain (**82**) resulted in an alternative dimeric iminoboronate species **83** being obtained (Scheme 36).[89]



Scheme 36 - Alternative dimeric iminoboronates from aliphatic imine diol 82

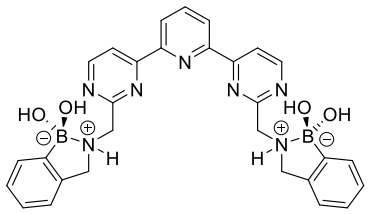
A variety of imine analogues were synthesised using all variations of the R and R_1 groups with their structures confirmed by NMR, mass spectroscopy and X-ray crystallography. The variation of the R and R_1 groups was seen to have no effect on the reaction pathway for product formation. These compounds were found to be more stable than those previously synthesised which contained no R substituents and an oxygen bridge between the two boron centres.[90]

In 2001, Anslyn *et al.* published a study into the effect of pH on N-B coordinate bonds by studying the structures observed for these complexes, which contained secondary or tertiary amine substituted boronic acids, at different pH (Scheme 37).[91]



Scheme 37 - Effect of pH on N-B coordinate bond formation

Anslyn used ^{11}B NMR spectroscopy to detect the N-B interaction. ^{11}B NMR spectroscopy is a useful technique for determining the structure of boron compounds since the shift of the boron resonance is greatly affected by the hybridisation of the boron centre. A purely tetrahedral sp^3 boron centre will have a resonance around 0 ppm whilst a purely trigonal planar sp^2 boron centre has a chemical shift of around 30 ppm. It was reported that the shift of the boron resonance changed from around 28 ppm at low pH to 8 ppm at a pH of 5.5. This demonstrates that boron changes hybridisation once the pH rises above 5.5 to a tetrahedral structure. At low pH the amine will be protonated and as the pH rises to 5.5 (pK$_{a1}$) and up to neutral the boron becomes tetrahedral and this can be assumed to be due to formation of the N-B interaction. In a rise to more basic pH (pK$_{a2}$) however, this tetrahedral structure can be accounted for by the two structures **84** and **85**, one of which incorporates an N-B interaction and the second of which incorporates an extra hydroxide. Further evidence for the N-B interaction at neutral pH was observed in the X-ray crystal structure of compound **86** which showed the presence of a tetrahedral boron centre, confirmed by ^{11}B NMR spectroscopy at 9.4 ppm, and a tetrahedral nitrogen centre (Figure 25).



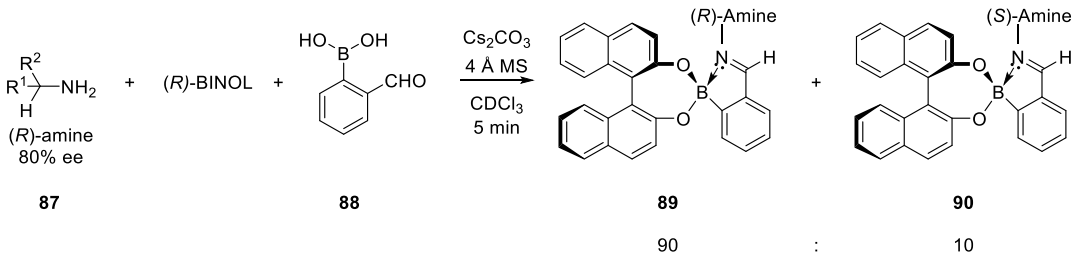
86

Figure 25 - Polyaza compound 86 as evidence for N-B interactions at neutral pH

Exploitation of these types of N-B interactions has been used to promote formation of boronate esters with 1,2- and 1,3- diols to develop fluorescent sensors for saccharides,[92] as well as in our groups research into NMR protocols for determining enantiomeric excess which will be discussed in the following sections.

2.2 Previous Work by the Group

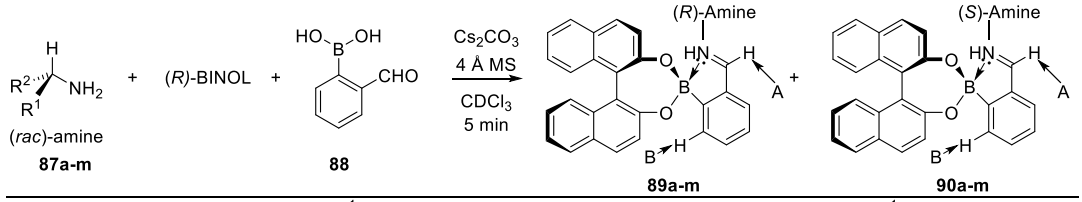
The Bull and James groups have developed a number of simple NMR protocols for the determination of enantiomeric excess of chiral molecules. In 2006, their groups published a simple three component protocol for determination of the enantiomeric excess of chiral primary amines.[93,94] This protocol involves derivatization of a chiral amine **87** with 2-formylphenylboronic acid **88** and enantiopure (*R*)-BINOL in $CDCl_3$ to quantitatively afford a mixture of diastereomeric iminoboronate esters **89** and **90** (Scheme 38).

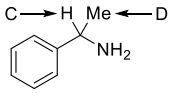
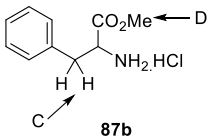
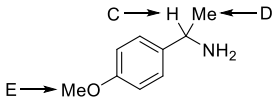
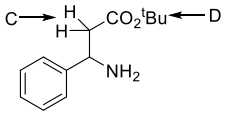
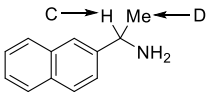
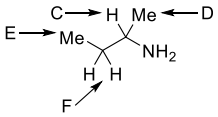
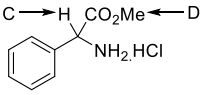
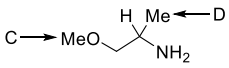
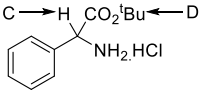
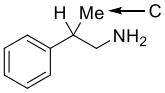
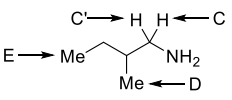
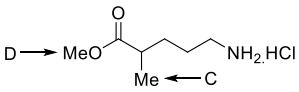
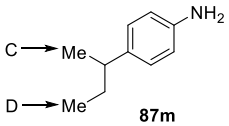


Scheme 38 - Bull-James protocol for determining the enantiomeric excess of chiral amines

From the ^{1}H NMR spectrum of the mixture of resultant iminoboronate complexes it is possible to accurately measure the integration of each peak of two diastereomeric protons, with the ratio of these integrations enabling the diastereomeric excess to be measured. As an enantiomerically pure diol is used, the enantiomeric excess of the amine determines the diastereomeric excess of the iminoboronate. Therefore, the enantiomeric excess of the amine can be inferred from the diastereomeric excess of the resulting complexes. Splitting of the diastereomeric imine proton was observed for almost all amines investigated. This is a useful feature of this protocol as this region of the ^{1}H NMR spectrum is free from any other resonances which could potentially overlap and hinder accurate integration. The imine signals are also removed from all other resonances associated with the diol fragment of the iminoboronate complex **89/90**, therefore acting as diagnostic signals for integration, independent of the amine being derivatized (Table 2).

Table 2 - Chemical Shift Differences (Δδ) in the 300 MHz ^{1}H NMR Spectra of 50:50 Mixtures of (*R*,*R*)-89a-m and (*R*,*S*)-90a-m Derived from Racemic Primary Amines 87a-m



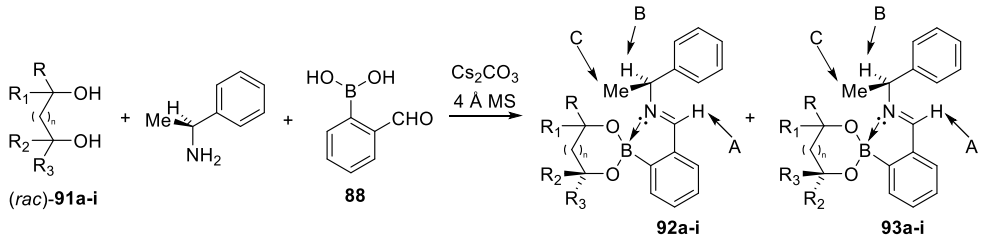
(*rac*)-amine	Δδ ^{1}H NMR (ppm)[a]	(*rac*)-amine	Δδ ^{1}H NMR (ppm)[a]
 **87a**	0.17 (A) -0.10 (C)[b] 0.21 (D)	 **87b**	0.39 (A) 0.19 (C) -0.34 (D)
 **87c**	0.20 (A) -0.11 (C) 0.21 (D) -0.15 (E)	 **87d**	0.38 (A) -0.12 (B) -0.20 (C) 0.19 (D)
 **87e**	0.17 (A) -0.09 (C)[c] 0.20 (D)	 **87f**	0.11 (C) 0.15 (D) -0.19 (E) -0.22 (F)
 **87g**	-0.05 (B) -0.02 (C) -0.52 (D)	 **87h**	-0.09 (A) 0.09 (B) -0.20 (C) 0.14 (D)
 **87i**	-0.43 (A) 0.10 (B) -0.05 (C) -0.67 (D)	 **87j**	-0.22 (C)
 **87k**	-0.08 (B) -0.31 (C) 0.30 (C') -0.11 (D) 0.40 (E)	 **87l**	0.04 (C)[de] 0.02 (D)[de]
 **87m**	0.02 (B)[e] 0.02 (C)[e] 0.03 (D)[e]		

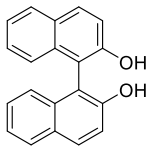
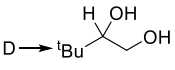
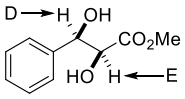
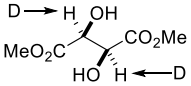
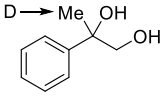
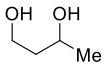
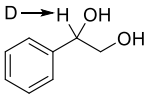
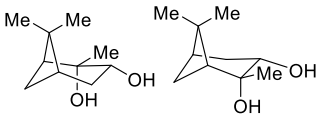
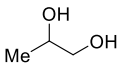
[a] A negative value indicated that the resonance corresponding to the (*R*,*R*)-diastereomer is more deshielded than the (*R*,*S*)-diastereomer. [b] The quartet corresponding to the methine proton of the (*R*,*R*)-**89a** diastereomer partially overlaps with the resonance of phenolic protons of residual (*R*)-BINOL; these signals no longer overlap on addition of 5 mol % of d_6-acetone to the NMR tube. [c] The quartet corresponding to the methine proton of (*R*,*S*)-**90e** partially overlaps with the resonance of penolic protons of residual (*R*)-BINOL. [d] ^{1}H NMR spectra recorded in d_6-acetone. [e] Unable to assign a sign to the Δδ values of these resonances because enantiopure samples of amines **87l** and **87m** were not available.

From Table 2 it can be seen that in all cases at least one pair of diastereomeric resonances were seen in the ^{1}H NMR spectra which could be used to determine the enantiomeric excess of the chiral amine, and in the majority of cases three or more pairs of diastereomeric resonances were potentially available for comparison. The derivatization protocol was able to determine the enantiomeric excess of a wide range of amines including those with remote stereocentres at carbons up to five bonds removed from the amine. Inspection of the ^{1}H NMR spectra of iminoboronate esters **89/90d**, **89/90g** and **89/90i** revealed that the *tert*-butoxy and methoxy resonances of the (*R*,*R*)-diastereomers were more deshielded than those of the corresponding (*R*,*S*)-diastereomers, indicating that the sign of the Δδ value could be used to determine the absolute configuration of α-amino esters. Similarly for diastereomeric iminoboronate esters **89/90a**, **89/90c** and **89/90e** comparison of the Δδ values for the imine, α-methyl and α-proton resonances revealed the same sign and magnitude of chemical shift difference, thus demonstrating that this derivatization protocol can be used to predict the absolute configuration of α-arylethylamines.

This same method could also be applied to determine the enantiomeric excess of chiral diols.[95,96] In this case, mixtures of iminoboronate complexes are formed from a chiral diol, 2-formylphenylboronic acid and enantiopure α-methylbenzylamine in $CDCl_3$ (Table 3). The enantiomeric excess of the chiral diol could then be measured by integration of a pair of diastereomeric protons in the ^{1}H NMR spectrum of the resultant mixture.

Table 3 - Chemical Shift Differences (Δδ) in the 400 MHz ^{1}H NMR Spectra of 50:50 Mixtures of (*S*,*R*)-92a-i and (*S*,*S*)-93a-i Derived from Racemic Diols 91a-i



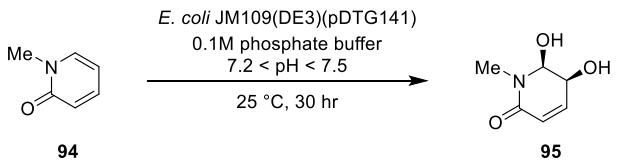
(*rac*)-diol	Δδ ^{1}H NMR (ppm)[a]	(*rac*)-diol	Δδ ^{1}H NMR (ppm)[a]
 **91a**	0.17 (A)[b] -0.10 (B)[b] 0.21 (C)[b]	 **91b**	0.07 (A)[c] 0.04 (D)[c]
 **91c**	-0.30 (A) -0.10 (B) 0.51 (D) 0.12 (E)	 **91d**	-0.31 (A) 0.12 (B) 0.28 (D)
 **91e**	0.07 (A)[c] 0.04 (D)[c]	 **91f**	0.02 (A)[b]
 **91g**	-0.07 (A)[b] -0.07 (D)[b]	 **91h**	-0.03 (A)
 **91i**	-0.03 (A)		

[a] A negative value indicates that the resonance corresponding to diastereomer **92** was more shielded than that of diastereomer **93**. [b] ^{1}H NMR spectra recorded in d_6-acetone. [c] Unable to assign a sign to the Δδ values of these resonances because enantiopure samples of diols **91b** and **91e** were not available.

Scalemic sampling studies revealed that both protocols were highly accurate, enabling the enantiomeric excess of chiral amines or diols to be determined within 2% of their known values.

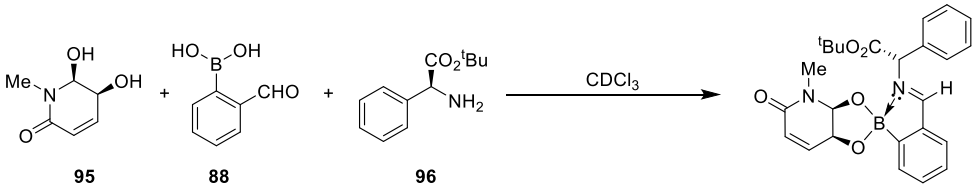
The use of this method has advantages over previously reported chiral derivatization agents. The most commonly used methods are those reported by Mosher[97] and Trost[17]. However, the Mosher method often requires the use of both ^{1}H NMR and ^{19}F NMR spectroscopy in order to accurately determine the enantiomeric excess of amines, whilst the Trost method requires the use of moisture sensitive acid chlorides to determine enantiomeric excess. Problems associated with kinetic resolution have also been found when using the Mosher method which could lead to the measurement of an inaccurate enantiomeric excess for a chiral substrate. The three component derivatization protocols reported by our group are experimentally simple to perform, as they involve the use of commonly available reagents, occur under ambient conditions and do not require rigorously anhydrous conditions. The diastereomeric iminoboronate complexes are formed in five minutes and enantiomeric excess can be determined quickly by ^{1}H NMR spectroscopy alone.

These two protocols have since been used by a number of groups for determination of the chirality and enantiopurity of chiral amines and diols produced as part of their syntheses. In 2008, Chopard *et al.* reported the formation of iminoboronate complexes to determine the enantiomeric excess of *cis*-dihydrodiols formed by dihydroxylation using *E. coli* JM109(DE3)(pDTG141) (Scheme 39).[98]



Scheme 39 - Enantioselective dihydroxylation of *N*-methyl-2-pyridone 94 to dihydrodiol 95

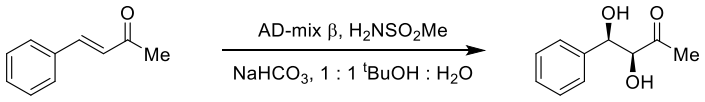
The ^{1}H NMR of the reaction between 2-formylphenylboronic acid **88**, (*R*)-phenylglycine *tert*-butyl ester **96** and dihydrodiol **95** (Scheme 40) confirmed formation of their product with an enantiomeric excess of >98% *e.e.*.



95 **88** **96**

Scheme 40 - Use of the Bull-James protocol to determine the enantiopurity of dihydrodiol 95

Anslyn *et al.* have reported the use of the Bull-James protocol a number of times to verify the enantiopurities of Sharpless dihydroxylation products (Scheme 41) that were synthesised as part of their studies into high throughput screening methods using indicator-displacement assays[99] and pattern-based recognition protocols.[100]



Scheme 41 – Representative Sharpless dihydroxylation reaction to form a diol

Anslyn synthesised a number of chiral diols in order to determine a high throughput screening method for evaluating the effectiveness of a number of chiral dihydroxylation catalysts. As part of this study, the enantiomeric excesses of all the diols employed in the study were determined by application of the Bull-James protocol.

In 2012, Inoue *et al.* published the total synthesis of four possible stereoisomers of resolvin E3 **98** (Figure 26).[101]

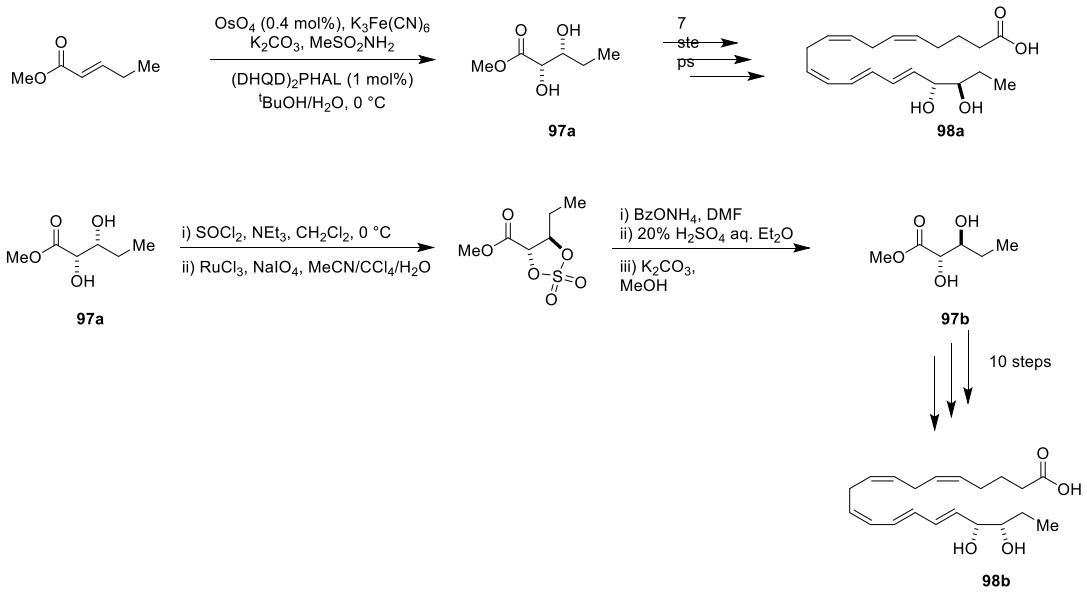
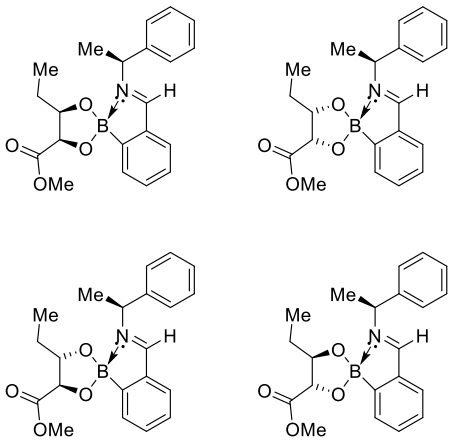


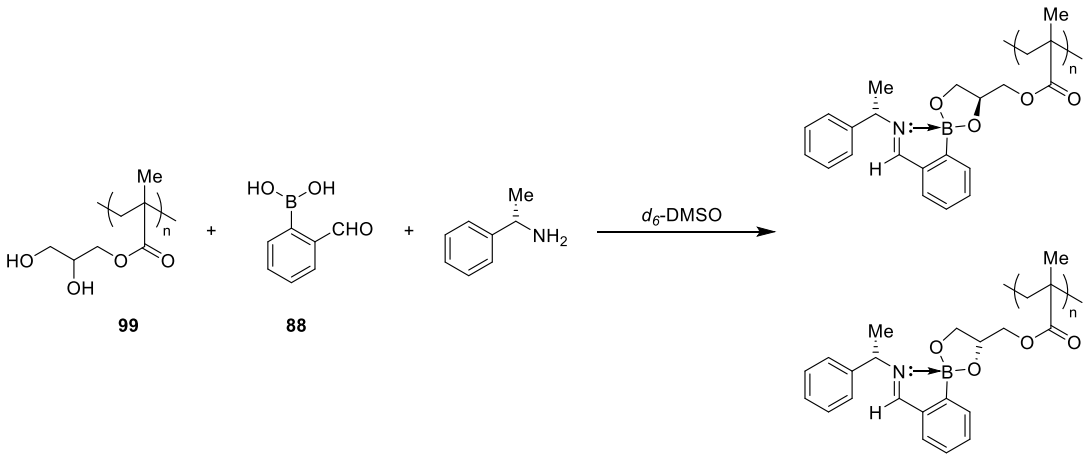
Figure 26 – Synthesis of the *syn*-98a and *anti*-98b diastereomers of resolvin E3 *via* diol intermediate 97

Inoue used the three component protocol to determine the enantiomeric excess of four chiral diol intermediates **97** formed in the synthesis of each diastereomer of resolvin E3, thus confirming the high stereoselectivity of their reported methodology (Scheme 42).



Scheme 42 - Enantiomeric excess of *syn*- and *anti*- diol intermediates 97 determined using the Bull-James protocol

Kressler *et al.* similarly used our reported diol protocol to determine the chirality of poly(glycerol methacrylate)s **99** (Scheme 43).[102]

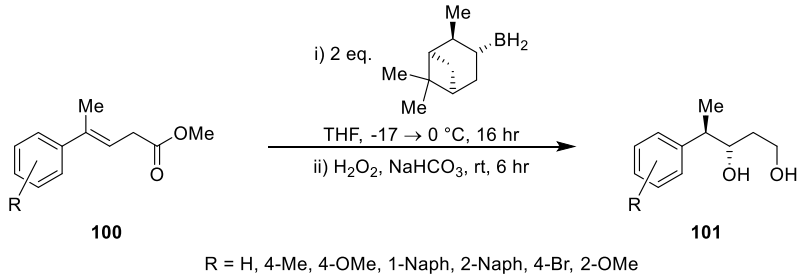


Scheme 43 - Determination of the chirality of poly(glycerol methacrylate)s 99 using the Bull-James protocol

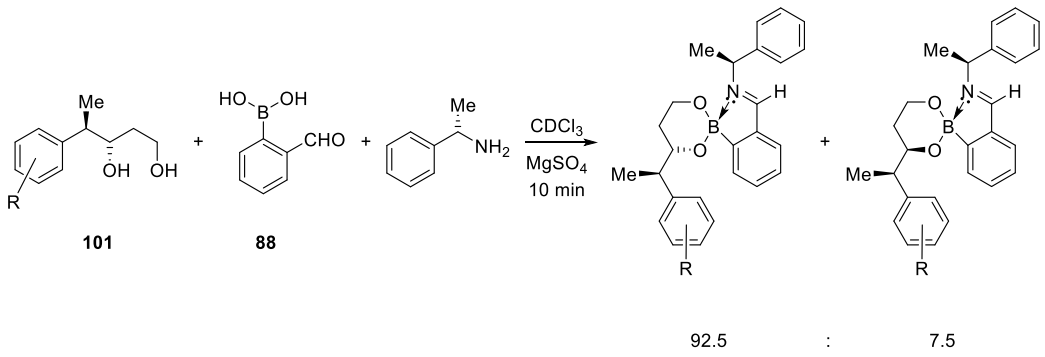
(*R*), (*S*) and (*rac*) samples of polymer **99** were shown to have identical ^{1}H NMR spectra. However, upon derivatization with 2-formylphenyl boronic acid **88** and (*S*)-α-methylbenzylamine the protons on the diastereomeric polymeric diol fragment

were shown to appear at different chemical shifts for the (*R*) and (*S*) polymer thus enabling the chirality of the polymer to be determined.

In 2013, Bull and Fordred reported the asymmetric synthesis of a range of chiral 1,3-diols **101** from the tandem asymmetric hydroboration/reduction reaction of trisubstituted β,γ-unsaturated esters **100** (Scheme 44) and determined the enantiomeric excess of the resultant 1,3-diols **101** using the three component coupling protocol (Scheme 45).[103]



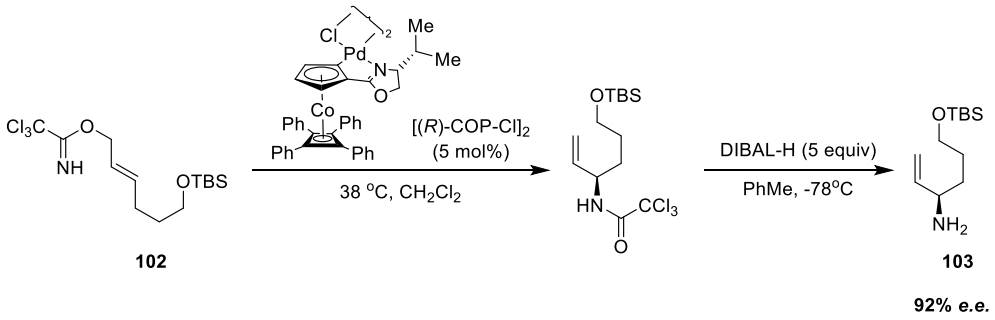
Scheme 44 - Asymmetric synthesis of chiral 1,3-diols 101 from trisubstituted β,γ-unsaturated esters 100



Scheme 45 - Determination of the enantiomeric excess of chiral 1,3-diols 101

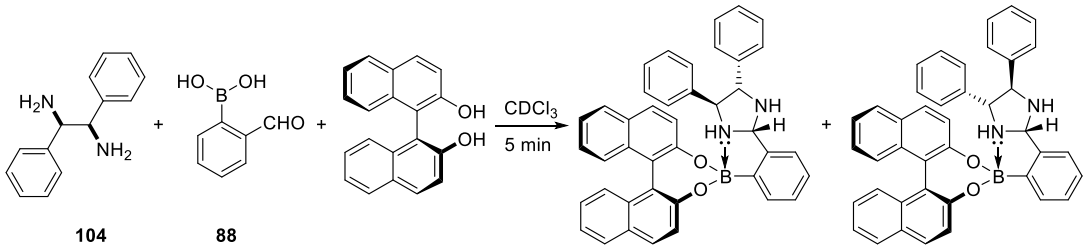
In 2011, Aldrich *et al.* employed the group's published method for determining the enantiomeric excess of chiral amines to evaluate the enantiopurity of amine **103** that

was formed from cobalt catalysed stereoselective [3,3]-rearrangement of allyl-trichloroacetimidate **102** (Scheme 46).[104]



Scheme 46 - Aldrich's synthesis of amine 84, *e.e.* determined by Bull-James protocol

In 2008, the Bull-James groups reported a protocol for determining the enantiomeric excess of chiral diamines using a similar three component coupling reaction (Scheme 47).[105]

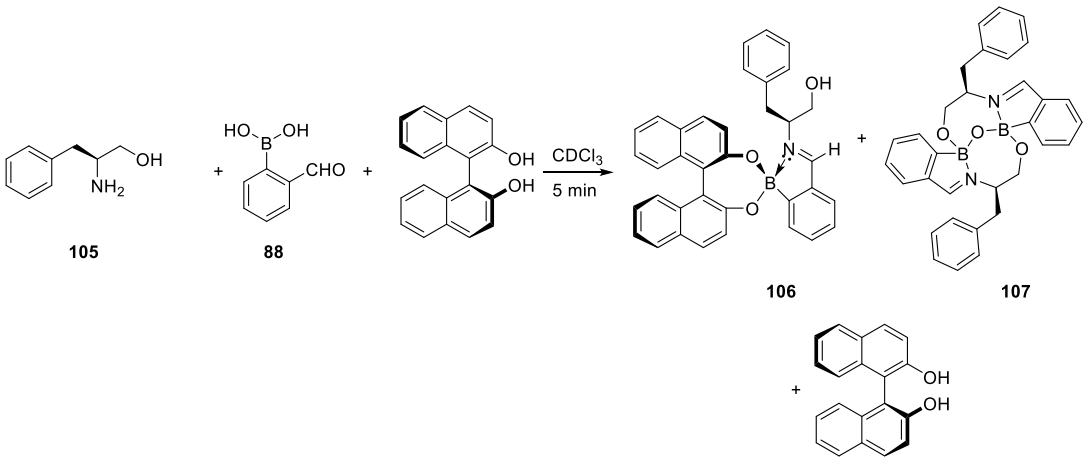


Scheme 47 – Bull-James protocol for determining the enantiomeric excess of chiral diamines

The ^{1}H NMR spectrum of the reaction between 1,2-diphenylethane-1,2-diamine, 2-formylphenylboronic acid and BINOL in $CDCl_3$ revealed the presence of diastereomeric imidazolidine complexes. Scalemic studies, using diamine **104** of known enantiomeric excess, validated this method as a protocol for determining the

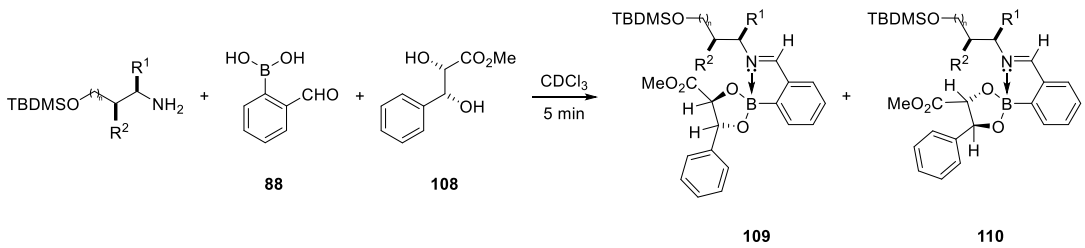
enantiomeric excess of these types of diamines. Enantiomeric excesses calculated from the ^{1}H NMR spectrum were within 4% of the known values, with baseline resolved resonances observed for a number of pairs of diastereomeric protons, making accurate integration easy.

A protocol for determining the enantiomeric excess of chiral β-amino alcohols was reported by the group in 2009.[106] It was first hypothesised that the same approach could be followed as used previously for primary amines[93,94] and diols.[95,96] However, it was found that addition of (*S*)-BINOL and 2-formylphenylboronic acid **88** to (*S*)-phenylglycinol **105** produced two different types of complexes (Scheme 48).



Scheme 48 – Formation of dimeric side products when the Bull-James protocol was initially applied to chiral unprotected 1,2-amino alcohols

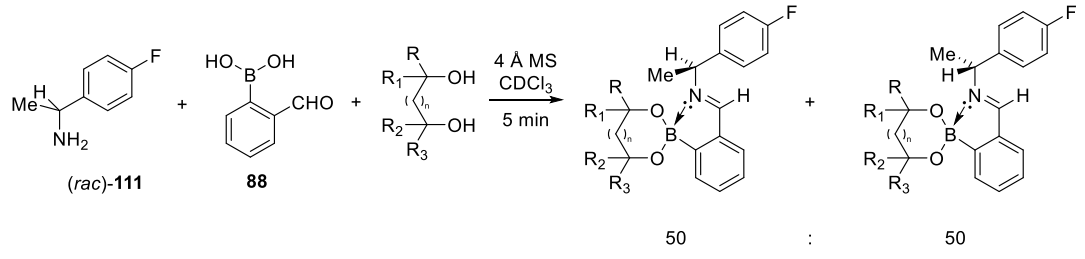
^{1}H NMR spectroscopy showed the expected iminoboronate ester **106**, boracycle species 10**7** and unreacted (*S*)-BINOL. Consequently, a modified protocol was devised in which the hydroxyl moiety of the amino alcohol was *O*-silyl protected using a *tert*-butyldimethylsilyl group and (*syn*)-methyl-2,3-dihydroxy-3-phenylpropionate **108** used as a chiral diol in place of BINOL (Scheme 49).



Scheme 49 – Bull-James protocol for determining the enantiomeric excess of chiral *O*-silyl-amino alcohols

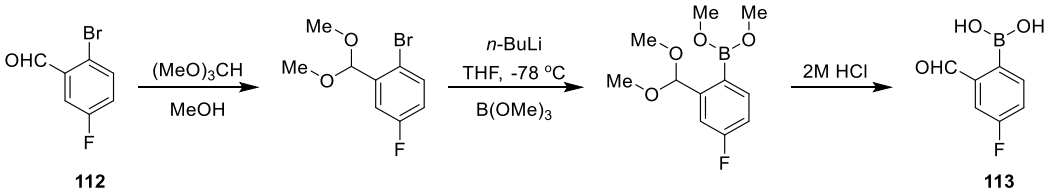
This led to quantitative formation of the desired iminoboronate esters **109** and **110** which enabled the enantiopurity of a range of scalemic samples of chiral amino alcohols, indicating that no dynamic kinetic resolution occurs, with baseline splitting of up to four distinct proton resonances observed.

The derivatization procedures discussed to this point have focussed on the use of ^{1}H NMR spectroscopy as the analytical tool with which to determine enantiomeric excess. However, in 2008, the group reported how ^{19}F NMR spectroscopy could also be used for determining the enantiomeric excess of chiral diols using this three component derivatization approach. The previously reported protocol for chiral diols[95,96] was adapted by using an enantiopure diol and (*rac*)-α-methyl-4-fluorobenzylamine **111** in place of α-methylbenzylamine (Scheme 50).[107]



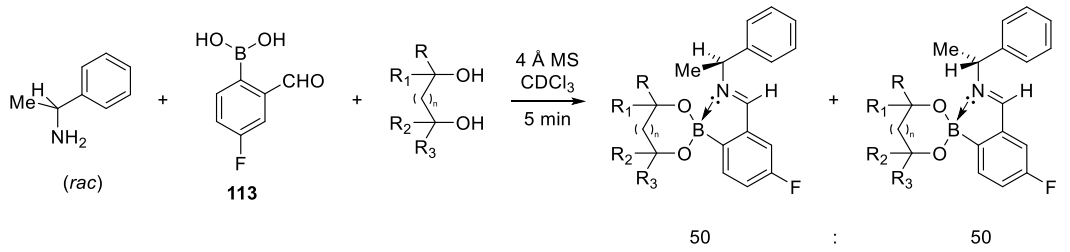
Scheme 50 - Determining the enantiomeric excess of chiral diols by ^{19}F NMR spectroscopy

Although the fluorine atom is in a relatively remote position, diastereomeric resonances were still seen in the ^{19}F NMR spectrum. However, the protocol using α-methyl-4-fluorobenzylamine **111** is clearly only able to be used to determine the enantiomeric excess of chiral diols and not chiral amines as the fluorine functionality is attached to the amine chiral auxiliary. In order to broaden the suitability of this protocol to be able to determine the enantiopurity of chiral amines, the fluorine functionality was incorporated into the boronic acid template by synthesis of 4-fluoro-2-formylphenylboronic acid **113** (Scheme 51).



Scheme 51 - Synthesis of fluorous 2-formylphenylboronic acid 113

The three-step synthetic route was designed to be simple, using commercially available 2-bromo-5-fluorobenzaldehyde **112** as a starting material which was also demonstrated to be amenable to large scale preparation. Fluorous boronic acid **113** was then treated with (*rac*)-α-methylbenzylamine and a range of chiral diols (Scheme 52). Inspection of both the ^{1}H and ^{19}F NMR spectra of the resultant 50:50 mixture of diastereomeric iminoboronate ester complexes showed baseline resolution for at least two pairs of diastereomeric resonances in the ^{1}H NMR spectra and a pairs of baseline resolved signals for the aryl-fluorine resonances of each diastereomer in the proton decoupled ^{19}F NMR spectra.



Scheme 52 – Determination of the enantiomeric excess of chiral amines and diols using fluorous 2-formylphenylboronic acid 113

The detection limits for this protocol were investigated through complexation of scalemic samples of methyl-(2*S*,3*R*)-dihydroxy-3-phenylpropionate of 80%, 90% and 98% with α-methylbenzylamine and 4-fluoro-2-formylphenylboronic acid. The values calculated from integration of the relevant diastereomeric resonances in the ^{1}H NMR spectra showed full agreement with the known enantiopurities of the starting diol of 80%, 90% and 98% respectively. Values calculated from the ^{19}F NMR spectrum also showed excellent accuracy with values of 80%, 90% and 96% obtained respectively.

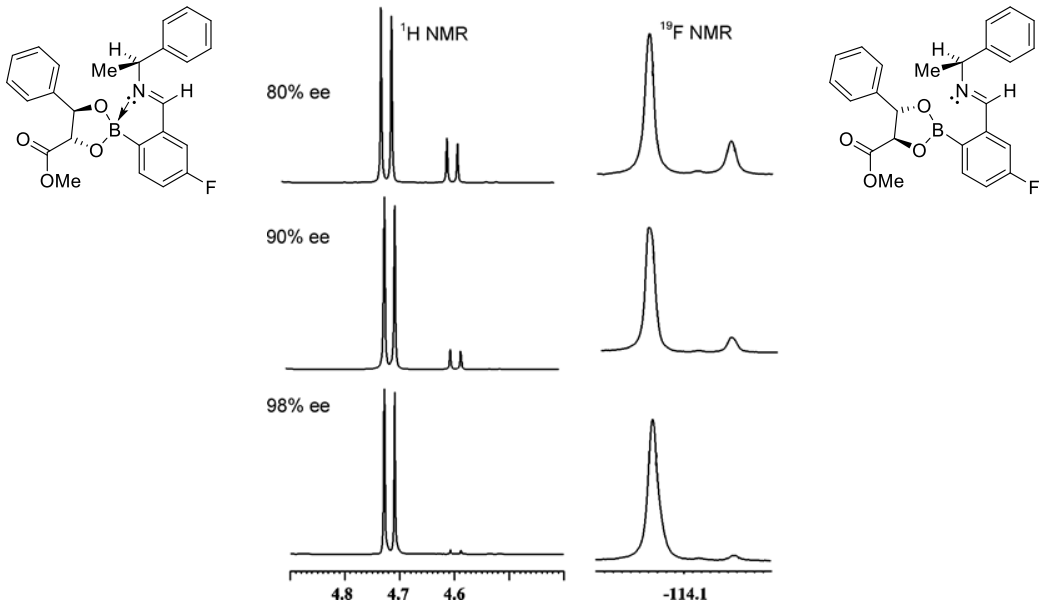
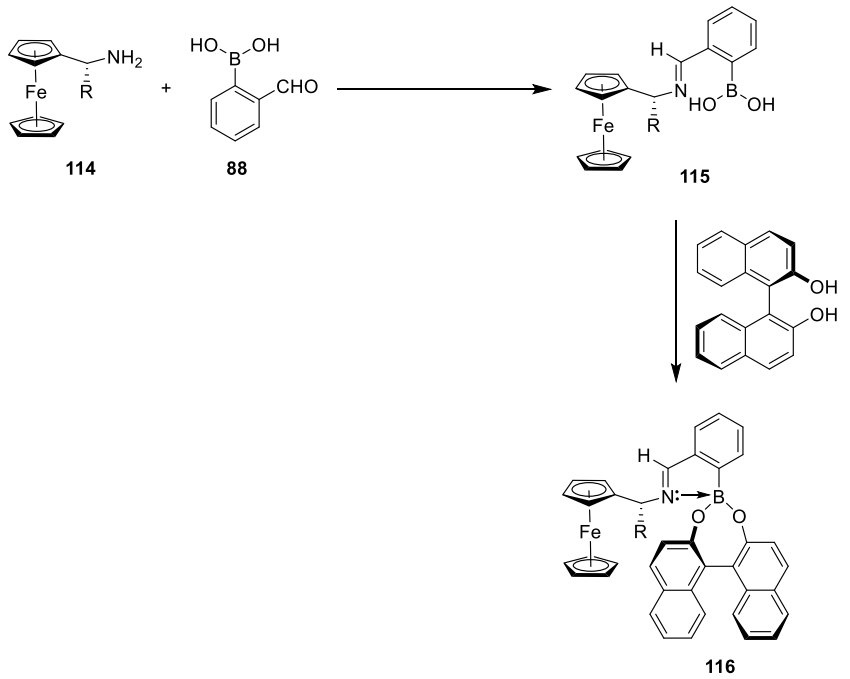


Figure 27 - Expansion of the ^{1}H NMR and ^{19}F NMR spectra of mixtures of the diastereomeric complexes prepared from derivatization of methyl-(2*S*,3*R*)-dihydroxy-3-phenylpropionate of 80%, 90% and 98% *e.e.*[107]

Whilst ^{1}H NMR spectroscopy is still extremely useful for determining the enantiomeric excess of chiral amines and diols, this protocol demonstrates that ^{19}F NMR spectroscopy can also be used either to validate the results obtained from ^{1}H NMR spectroscopy, or as a complimentary analytical tool due to its comparable accuracy.

In 2010, in collaboration with Tucker *et al.*, the group developed an electrochemical method for determining enantiomeric excess using a variation of the three component coupling method (Scheme 53).[108]



Scheme 53 - Enantiomeric excess determination by electrochemical analysis of iminoboronate ester complexes derived from ferrocene

An electrochemically active coupling protocol was devised using chiral ferrocenyl amine **114** as a redox active amine to react with 2-formylphenylboronic acid **88** and BINOL to form the three component complex **116**. It was reported that the configuration of the benzylic position adjacent of the chiral ferrocene auxiliary controlled the strength of the binding of BINOL enantiomers to the boronic acid. When the benzylic position had an (*R*) geometry, (*R*)-BINOL was more strongly bound to the complex than the (*S*) enantiomer. The opposite case was also found to be true, an (*S*) benzylic geometry resulted in (*S*)-BINOL binding more strongly than (*R*)-BINOL. Square wave voltammetry revealed electrochemical discrimination between the (*R*) and (*S*)-BINOL enantiomers since the (*R*,*R*)-complex showed a larger positive shift in electrode potential when compared to the (*R*,*S*)-complex (Figure 28).

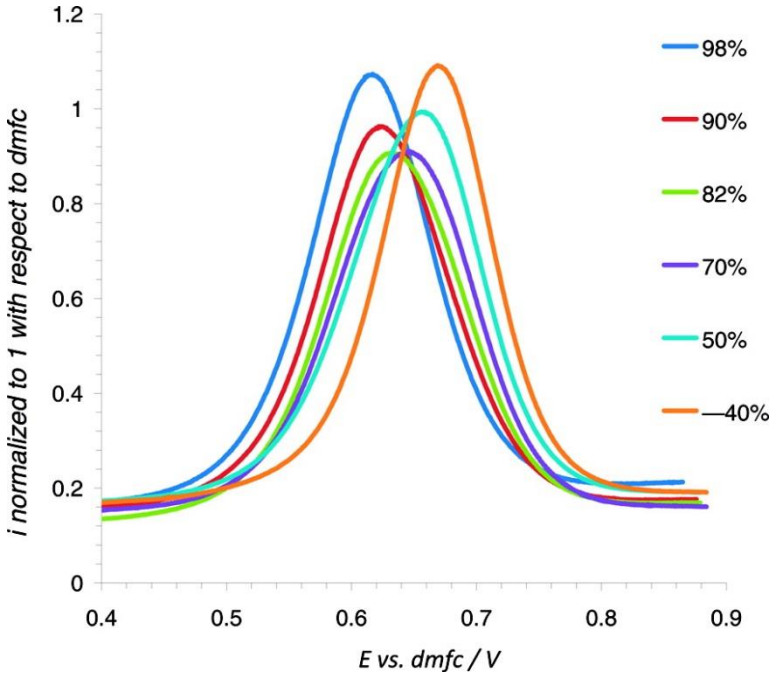


Figure 28 - Square wave voltammograms of (*R*)-115 in the presence of a 10-fold excess of BINOL of varying enantiomeric excess, *e.e.* expressed as % relative to (*S*)-BINOL[108]

Scalemic sampling showed a gradual positive shift in electrode potential as the enantiomeric excess of (*R*)-BINOL increased and a linear relationship between enantiomeric excess and observed electrode potential between 60% and 98% *e.e.*, indicating that these redox active complexes could be used to determine enantiomeric excess (Figure 29).

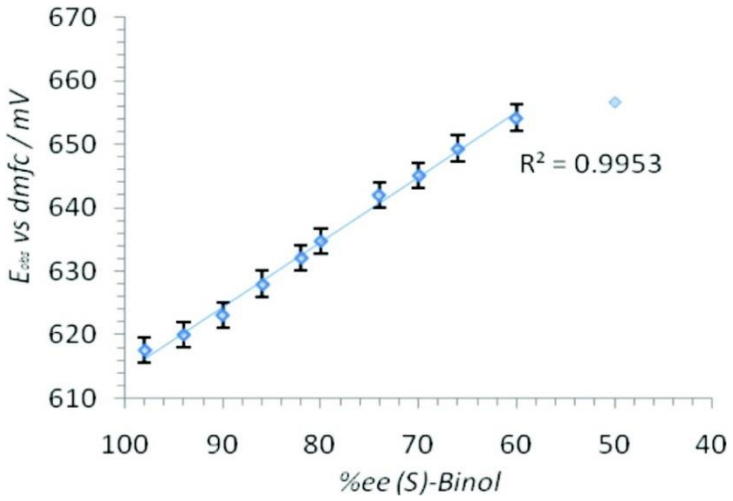
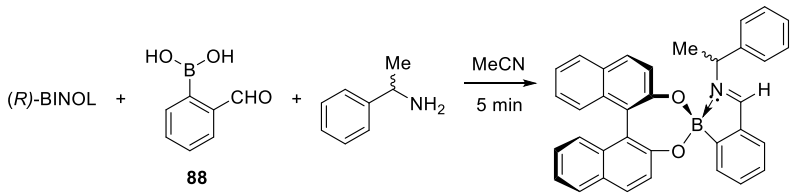


Figure 29 - Calibration curve showing linear dependence of E_{obs} against % *e.e.* of (*S*)-BINOL between 60% and 98% *e.e.*[108]

Subsequently, collaboration with the Anslyn group led to publication of a circular dichroism method for determining the enantiomeric excess of α-chiral amines using the three component coupling protocol (Scheme 54).[109]



Scheme 54 - Three component coupling reaction between (*R*)-BINOL, 2-formylphenylboronic acid 88 and α-methylbenzylamine

It was reported that the CD spectrum of the reaction between 2-formylphenylboronic acid **88**, (*S*)-BINOL and α-methylbenzylamine showed a difference in response to the presence of the (*R*) and (*S*) enantiomers of the amine. Generation of a calibration curve using samples of known enantiomeric excess of

chiral amine showed a linear relationship between CD response and enantiomeric excess (Figure 30).

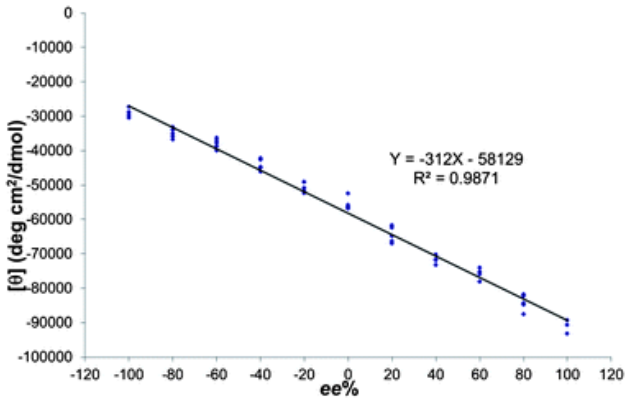
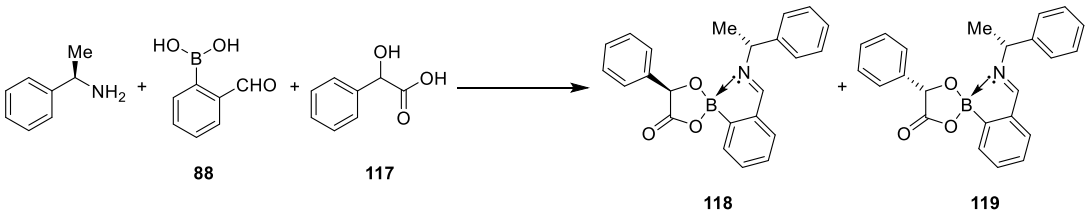


Figure 30 - Calibration curve developed by Anslyn depicting the change in CD response with enantiomeric excess[109]

Using a linear equation for the line of best fit it proved possible to determine the enantiomeric excess of an unknown sample of chiral amine based on the measured CD response at 240 nm after three component derivatization. It was noted that the method was most accurate when determining higher levels of enantiomeric excess (to within 1.8%). Although accuracy decreased at lower levels of enantiomeric excess, these values are normally less important when attempting to optimize an asymmetric protocol. This CD procedure was also shown to be valid for a range of α-chiral primary amines as well as α-methylbenzylamine.

Recently, Suryaprakash and co-workers have employed our three-component protocol for the determination of the enantiomeric excess of α-hydroxy acids.[110] By formation of an iminoboronate ester complex from 2-formylphenylboronic acid **88**, enantiopure α-methylbenzylamine and a chiral α-hydroxy acid **117** it was demonstrated that the enantiopurity of the α-hydroxy acid could be determined from the ^{1}H NMR spectrum of the resultant iminoboronate ester complexes **118** and **119** (Scheme 55).



Scheme 55 – ^{1}H NMR protocol for determination of enantiomeric excess of chiral α-hydroxyacids

Suryaprakash showed that the shifts for a number of protons in the ^{1}H NMR spectra for each of the pair of diastereomeric complexes **118** and **119** formed in the three-component coupling reactions differed sufficiently such that accurate integration of these resonances could be used to calculate the enantiomeric excess of the α-hydroxy acid employed.

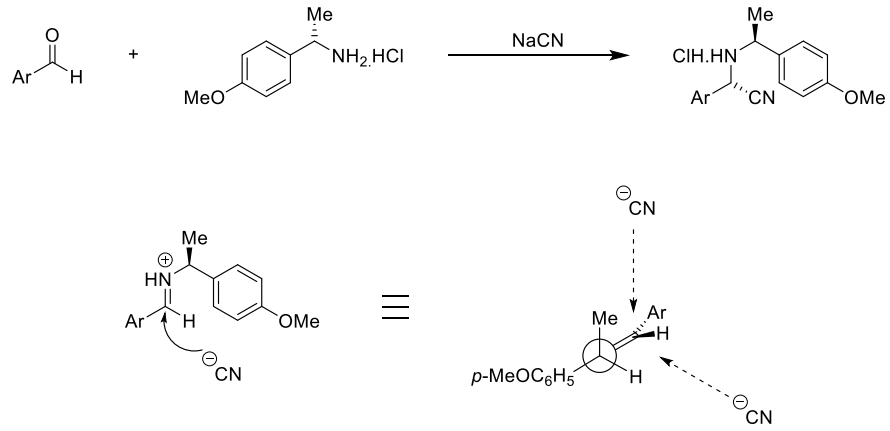
2.3 Results and Discussion

This chapter has discussed the various methods for determining the enantiomeric excess of chiral substrates using the three-component methods developed by the Bull-James group that employed NMR spectroscopic analysis of diastereomeric complexes to determine the enantiomeric excess of chiral molecules. The discussion will now focus on the development of a simple synthetic protocol for the synthesis of α-arylglycines and the determination of their enantiomeric excess using this simple boronic acid based derivatization methodology.

2.3.1 Auxiliary Controlled Strecker Syntheses of α-Arylglycines

The Strecker reaction is often the chosen route for the synthesis of α-amino nitriles which can be hydrolysed to amino acids.[111,112] This is due to the relative experimental simplicity and wide substrate scope of the reaction. There has been much research into stereoselective catalytic variants of the reaction, with both metal

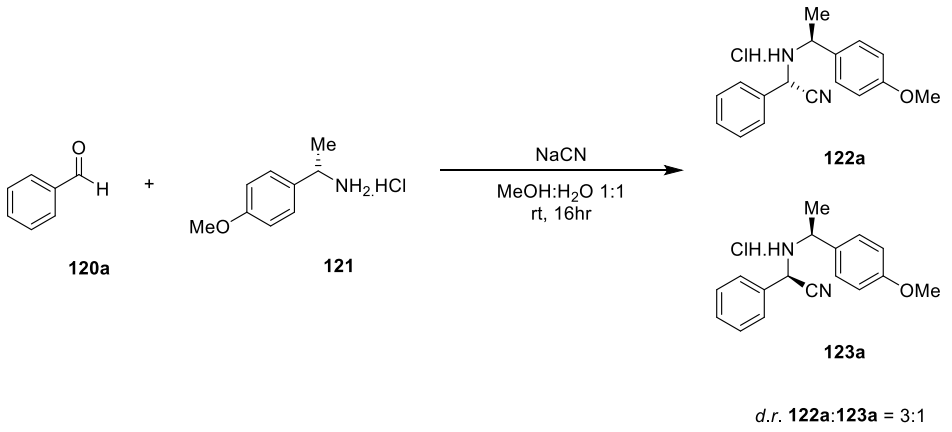
based catalysts[113] and organocatalysts[114,115] being employed. As an alternative to chiral catalysts, we decided to investigate the use of chiral auxiliaries in the Strecker reaction. The use of α-methylbenzylamine as a chiral auxiliary for the Strecker reaction was first proposed by Harada.[116] We decided to investigate the use of (*S*)-1-(4-methoxyphenyl)ethanamine hydrochloride **121** as a chiral auxiliary since, this auxiliary can be cleaved simply with acid hydrolysis and could provide steric bulk to direct the incoming cyanide anion to preferentially attack the *Si* face of the intermediate iminium ion formed from reaction of (*S*)-1-(4-methoxyphenyl)ethanamine hydrochloride **121** and an aryl aldehyde. The selectivity of the chiral auxiliary can be explained by consultation of the conformational model shown in Scheme 56.



Scheme 56 - Conformational model for the auxiliary controlled addition of cyanide to an intermediate iminium ion

In this model the lowest energy conformer would be that involving the proton and aryl substituents of the iminium bond being straddled by the methyl and proton of the (*S*)-1-(4-methoxyphenyl)ethanamine fragment. As the cyanide anion approaches along the Bürgi-Dunitz angle of 107° the *Re* face of the iminium bond is partially blocked by the positioning of the methyl group, thus there will be some directing of the cyanide ion towards the *Si* face generating (*S*,*S*)-α-amino nitrile.

In a variant of the reported literature procedure[117,118] benzaldehyde **120a** was treated with (*S*)-1-(4-methoxyphenyl)ethanamine hydrochloride **121** and sodium cyanide in H_2O:MeOH (1:1) and the resultant solution stirred for 16 hours at room temperature (Scheme 57). The hydrochloride salt of the chiral auxiliary was used since initial attempts using the free auxiliary resulted in relatively low yields.

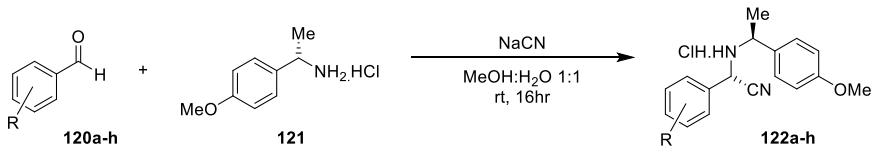


Scheme 57 – Chiral auxiliary controlled Strecker synthesis to form α-amino nitrile 122a

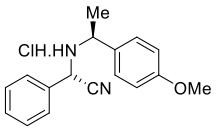
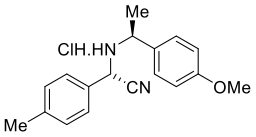
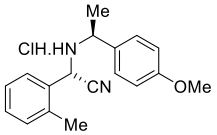
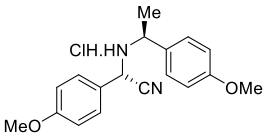
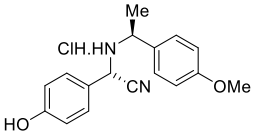
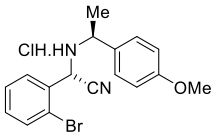
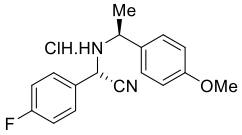
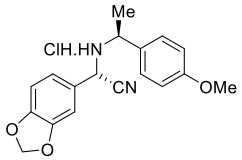
^{1}H NMR spectroscopic analysis of the crude reaction mixture showed that the α-amino nitrile product was formed in a 3:1 diastereomeric ratio in favour of the (*S*,*S*)-**122a** diastereomer by integration of the α-proton resonance. Purification of the major diastereomer, (*S*,*S*)-**122a** was achieved by recrystallization of the crude reaction mixture from saturated methanolic HCl and diethyl ether, giving (*S*,*S*)-**122a** in a >99:1% diastereomeric ratio and 62% yield.

This Strecker procedure was then successfully applied to a range of aryl-substituted benzaldehydes **120b-h** which resulted in the formation of their respective α-amino nitriles **122b-h** in diastereomeric ratios of >95:5 (Table 4).

Table 4 – Chiral auxiliary controlled asymmetric Strecker reactions for the synthesis of α-amino nitriles 122a-h



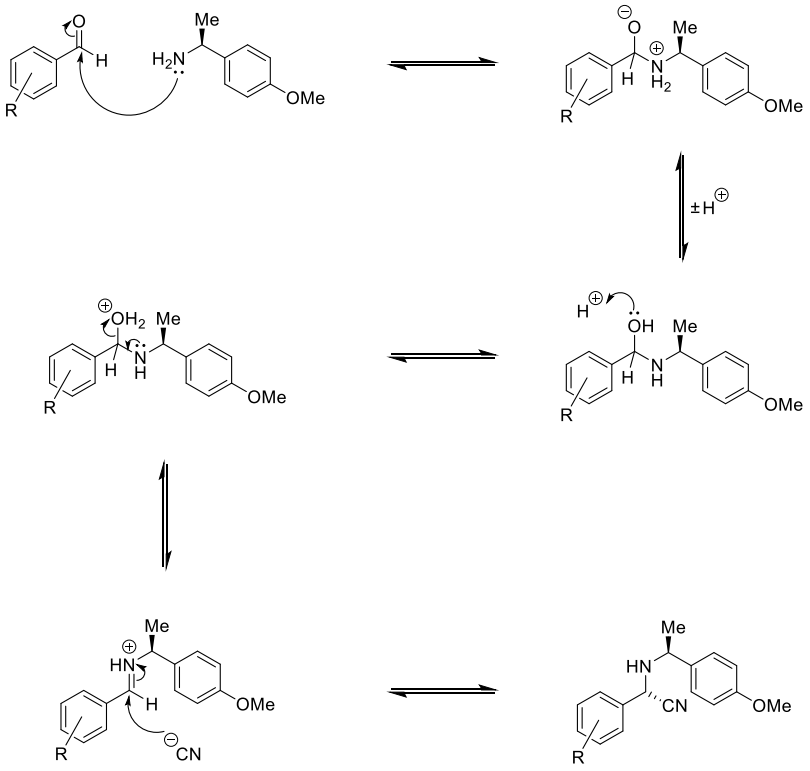
a) R = H, b) R = 4-Me, c) R = 2-Me, d) R = 4-MeO, e) R = 4-OH, f) R = 2-Br, g) R = 4-F, h) R = 3,4-(OCH_2O)

entry	(*S*,*S*)-α-amino nitrile	yield (%)	*d.r.* (**122**:**123**)[a]
1		62	>99:1[b]
2		77	>99:1
3		60	>99:1
4		87	>99:1
5		86	>99:1
6		58	95:5
7		70	>99:1[b]
8		54	>99:1[b]

[a] Determined by ^{1}H NMR spectroscopic analysis. [b] Obtained after recrystallization of the crude product from saturated methanolic HCl and diethyl ether.

It was found that for the Strecker reactions of substituted benzaldehydes **120b-f**, the resultant α-amino nitriles were formed as 3:1 mixtures of diastereomers from which the major (*S*,*S*)-α-amino nitrile diastereomer precipitated out of the reaction mixture and was able to be collected by filtration in a >99:1 diastereomeric ratio without need for further purification. However, for benzaldehydes **120g,h** this was not the case and crystalline precipitates were not afforded. However, the major (*S*,*S*)-α-amino nitrile diastereomers **122g,h** were purified *via* fractional crystallization of their crude reaction mixtures (77:23 and 80:20 *d.r.* respectively) from saturated methanolic HCl and diethyl ether in a >99:1 diastereomeric ratio.

In this process an iminium species is formed between the aldehyde and amine auxiliary which subsequently undergoes stereoselective nucleophilic attack by a cyanide nucleophile (Scheme 58).



Scheme 58 - Mechanism for the three-component formation of an α-amino nitrile[119]

The relative configuration of *p*-tolyl substituted α-amino nitrile **122b** in relation to the (*S*)-1-(4-methoxyphenyl)ethanamine hydrochloride **121** of known absolute configuration was assigned by X-ray crystallographic analysis (Figure 31).

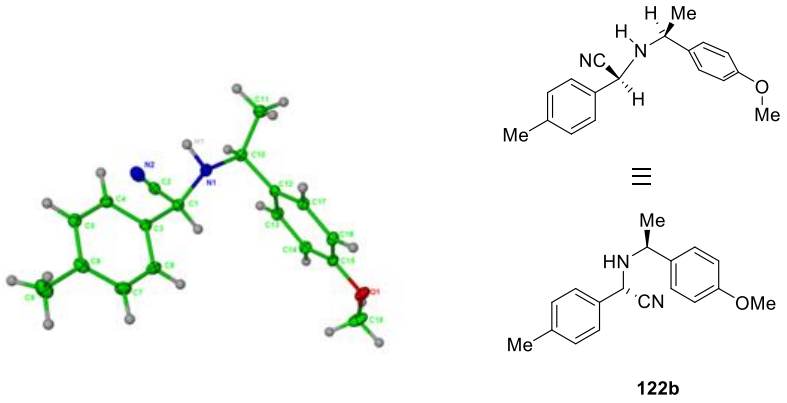


Figure 31 - X-ray crystal structure of (*S*,*S*)-*p*-tolyl-α-amino nitrile 122b

X-ray crystallographic analysis revealed the presence of intermolecular hydrogen bonding within the crystal lattice between the amine proton and the lone-pair of the nitrile moiety (Figure 32).

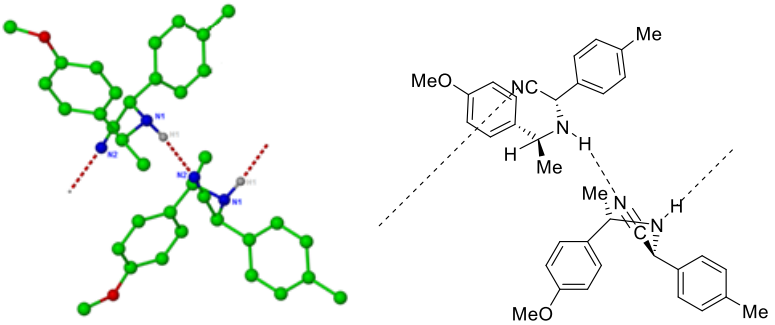
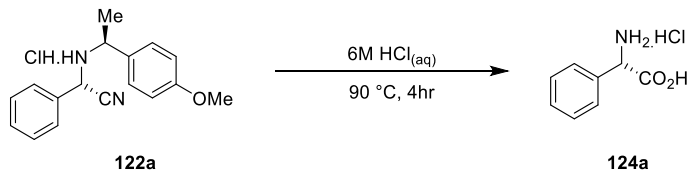


Figure 32 - Hydrogen bonding between amine and nitrile groups in the crystal structure of (*S*,*S*)-*p*-tolyl-α-amino nitrile 122b

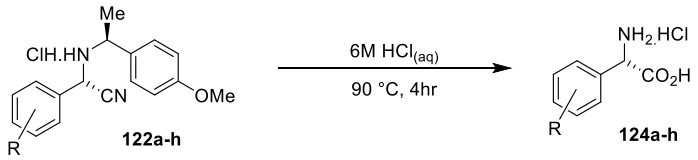
For the removal of the chiral auxiliary fragment, it had previously been reported that trifluoroacetic acid[120] or formic acid/triethylsilane[121,122] could be used to cleave the *N*-1-(4-methoxyphenyl)ethyl fragment. Thus, it was theorized that aqueous acidic conditions would be sufficient for removal of the auxiliary fragment from α-amino nitriles **122a-h** whilst concomitantly hydrolysing their nitrile groups to afford the corresponding α-arylglycines in one-pot. Thus, (*S*,*S*)-α-amino nitrile **122a** was heated at reflux in 6M hydrochloric acid for 4 hours which resulted in both hydrolysis of the nitrile moiety, and cleavage of the *N*-1-(4-methoxyphenyl)ethyl auxiliary fragment to afford crude (*S*)-α-phenylglycine hydrochloride **124a** (Scheme 59).



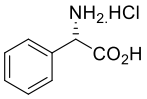
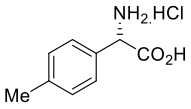
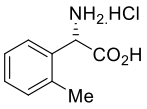
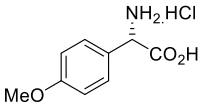
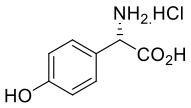
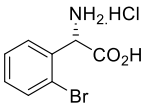
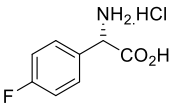
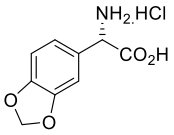
Scheme 59 - Concomitant hydrolysis and deprotection of α-amino nitrile 124a

The crude product was purified by suspending the reaction mixture in chloroform and filtering the resultant suspension to yield (*S*)-α-phenylglycine hydrochloride **124a** as a white solid in a 60% yield. The absolute configuration of (*S*)-α-phenylglycine **124a** was confirmed by comparison of the negative sign of its specific rotation with that of commercially available (*S*)-α-phenylglycine. This hydrolysis and deprotection protocol was then applied to α-amino nitriles **122b-h** to afford their corresponding α-arylglycines **124b-h** in moderate yields (52-81%) and high enantiomeric excess (88-96%) (Table 5).

Table 5 - Hydrolysis and deprotection of α-amino nitriles 122a-h to α-arylglycines 124a-h

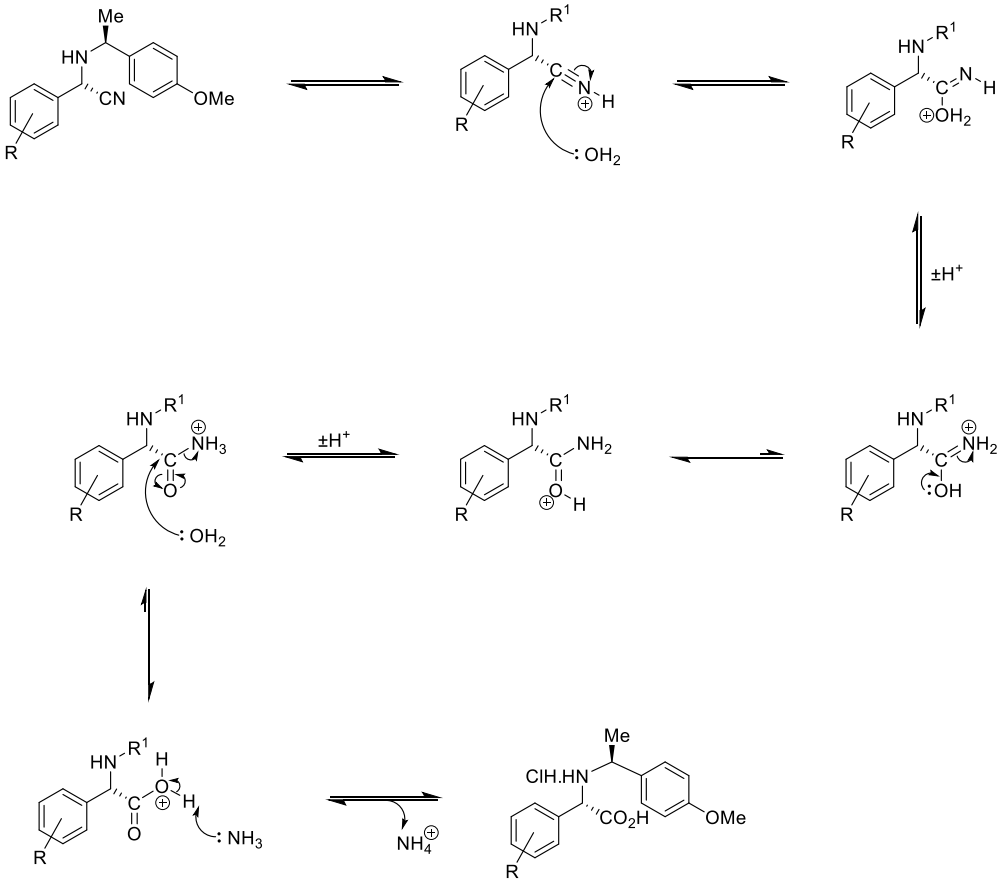


a) R = H, b) R = 4-Me, c) R = 2-Me, d) R = 4-MeO, e) R = 4-OH, f) R = 2-Br, g) R = 4-F, h) R = 3,4-(OCH_2O)

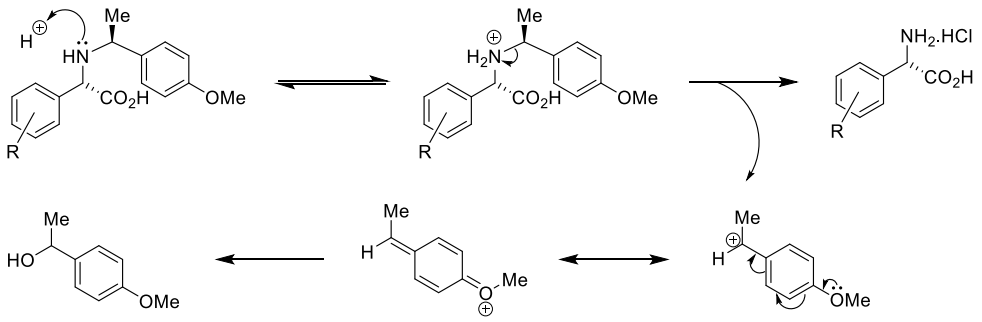
entry	α-arylglycine	yield (%)	*e.e.* (%)
1		60	96
2		56	94
3		80	95
4		52	90
5		81	94
6		80	95
7		63	96
8		64	88

[a] *e.e.* determined by ^{1}H NMR spectroscopic analysis of the iminoboronate complexes formed from derivatization of the corresponding methyl esters using 2-formylphenylboronic acid and (*S*)-BINOL.

In this process the hydrolysis and deprotection steps are likely to occur in tandem due to the excess of aqueous acid present, however, for simplicity the relevant mechanisms are shown separately in Scheme 60 and Scheme 61.

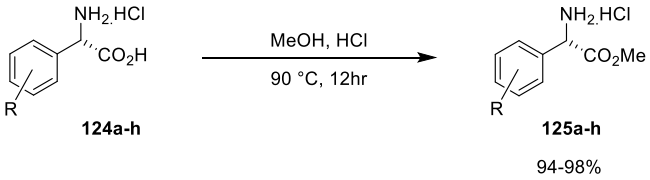


Scheme 60 - Hydrolysis of a nitrile group to a carboxylic acid



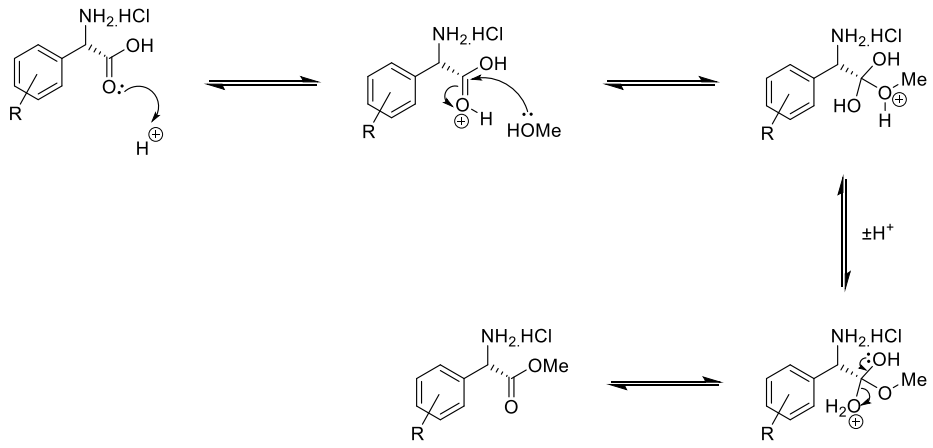
Scheme 61 - Hydrolysis of the *N*-1-(4-methoxyphenyl)ethyl auxiliary fragment by acid hydrolysis

It has been previously reported that acid hydrolysis of an α-amino nitrile can lead to some racemisation of the α-centre of the α-arylglycine product.[123] As a result of this, it was decided to determine the enantiomeric excess of α-arylglycines **124a-h** using our published chiral derivatization protocol.[93,94] In order to determine the enantiomeric excess of these α-arylglycines they were first converted to their corresponding methyl esters in a quantitative yield by refluxing in hydrochloric acid and methanol (Scheme 62), a process known to proceed without racemisation.



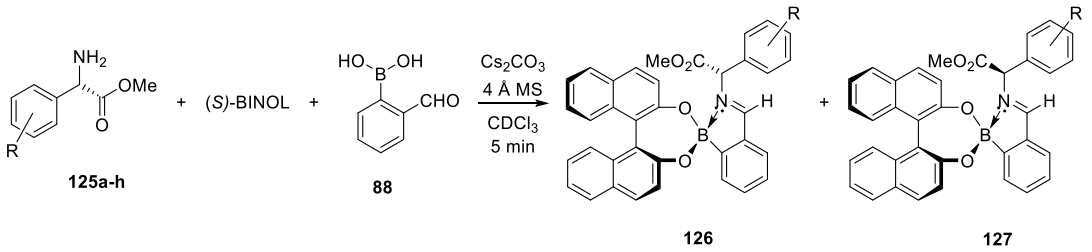
a) R = H, b) R = 4-Me, c) R = 2-Me, d) R = 4-MeO, e) R = 4-OH, f) R = 2-Br, g) R = 4-F, h) R = 3,4-(OCH_2O)

Scheme 62 - Synthesis of methyl esters 125a-h from their parent α-arylglycines 124a-h



Scheme 63 – Mechanism of conversion of an α-arylglycine to its corresponding methyl ester

Amino esters **125a-h** were then treated with 2-formylphenylboronic acid **88**, (*S*)-BINOL and caesium carbonate in deuterated chloroform using our previously reported optimum conditions (Scheme 64).



Scheme 64 - Derivatization of α-arylglycine methyl esters 125a-h using the Bull-James protocol

This resulted in formation of mixtures of diastereomeric iminoboronate complexes **126** and **127** whose ratio was determined by integration of the appropriate baseline separated diastereomeric resonances in their ^{1}H NMR spectrum. The ^{1}H NMR spectra obtained from the mixtures of diastereomeric complexes from derivatization of amino ester **125a** with 2-formylphenylboronic acid **88**, caesium carbonate and *rac*-BINOL and (*S*)-BINOL respectively can be seen in Figure 33.

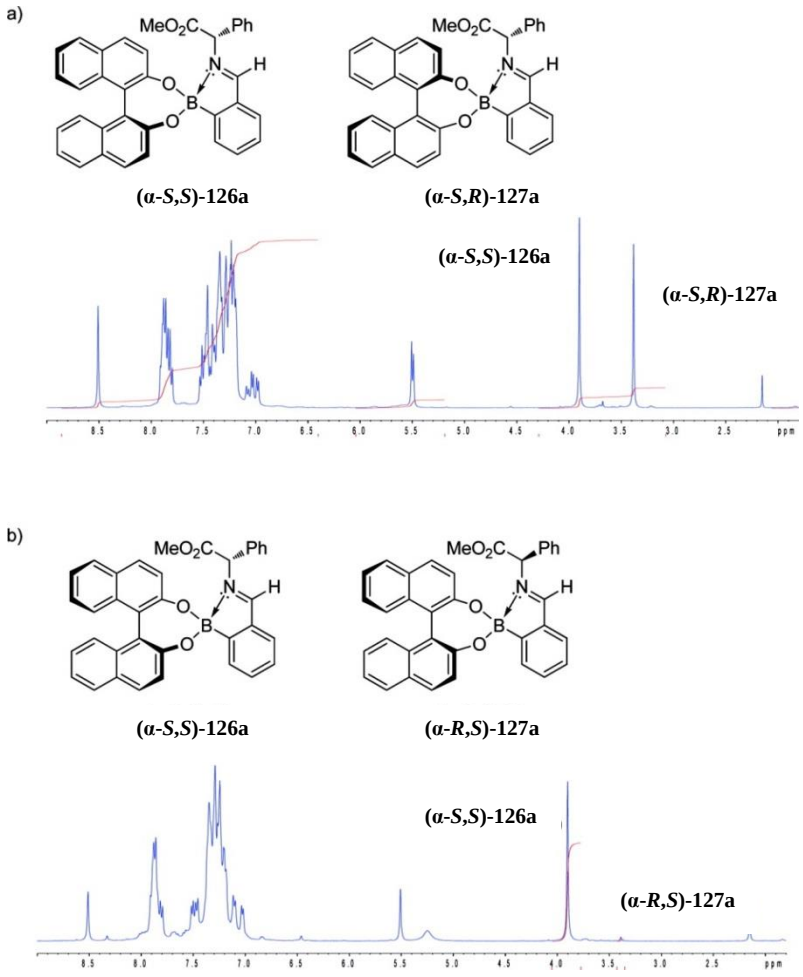
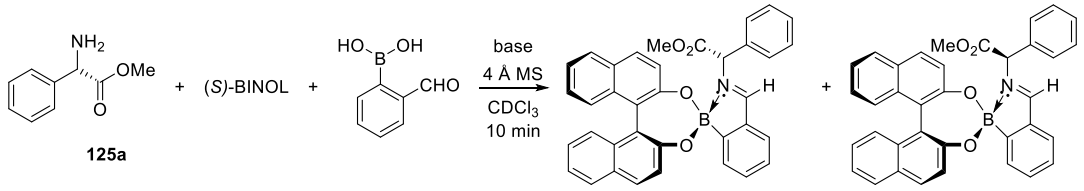


Figure 33 – ^{1}H NMR spectra obtained from derivatization of amino ester 125a a) with 2-formylphenylboronic acid 88, *rac*-BINOL and Cs_2CO_3 and b) with 2-formylphenylboronic acid 88, (*S*)-BINOL and Cs_2CO_3. Proton resonances of the methyl ester resonances used for *e.e.* determination

Analysis of the resultant ^{1}H NMR spectrum for the derivatization of amino ester **125a** with *rac*-BINOL (Figure 33) revealed that unlike with our previously reported diol derivatization protocol where the imine proton resonance was a useful diagnostic resonance for determining enantiomeric excess, here, the imine resonance was not resolved and the α-proton resonance at 5.5ppm was only partially resolved. However, a large Δδ of around 0.5ppm was revealed for the well resolved methoxy resonance which was used for enantiomeric excess determination. This enabled us to determine that all of the α-arylglycine methyl esters produced using our asymmetric Strecker reaction had been produced in >95% enantiomeric excess.

Although the Bull-James protocol has been employed by a number of groups to determine the enantiomeric excess of a wide range of chiral amines (as discussed above) in 2009 Urriolabeitia *et al.* reported that racemization occurred when this protocol was applied to commercially available (*R*)-phenylglycine methyl ester.[124] In order to reinvestigate their report, we derivatized commercially available (*S*)-α-phenylglycine methyl ester hydrochloride of known 98% enantiomeric excess with 2-formylphenylboronic acid and (*S*)-BINOL. It was decided to investigate the role of the base and time in the derivatization protocol, since it was postulated that if the caesium carbonate is left in the reaction mixture for prolonged periods then epimerisation of the α-centre of the (*S*)-α-phenylglycine methyl ester might occur. Potassium carbonate was employed as an alternative to caesium carbonate since it is less soluble in chloroform, and less likely to result in unwanted epimerisation (Table 6).

Table 6 - Investigating the effect of base and reaction time on epimerisation of iminoboronate complexes 126a and 127a



entry	base	reaction time[a]	^{1}H NMR aquisition time	*d.r.* (**126a**:**127a**)[b]
1	Cs_2CO_3	10 min	10 min	99:1
2	Cs_2CO_3	5 hr	5 hr	94:6
3	Cs_2CO_3	24 hr	24 hr	53:47
4	K_2CO_3	10 min	10 min	99:1
5	K_2CO_3	10 min	24 hr	99:1

[a] Reaction time until filtering excess base. [b] *d.r.* determined by ^{1}H NMR spectroscopic analysis

The results in Table 6 show that when the ten minute reaction time suggested in the original publication of our protocol is followed that there is no evidence of any

epimerisation at the α-centre of the (*S*)-α-phenylglycine methyl ester since the measured *d.r.* from the ^{1}H NMR spectroscopic analysis directly correlates with the expected 98% *e.e.* of the commercial (*S*)-α-phenylglycine methyl ester. However, when the reaction was left to run for prolonged periods of time, such as for entries 2 (5 hrs) and 3 (24 hrs) in Table 6, partial racemisation of the α-centre occurred. In fact, after a 24 hour period, the measured diastereomeric ratio shows that the methyl ester has been epimerised to such a degree that it has become essentially a 50:50 mixture. When potassium carbonate was employed as base in the derivatization protocol, clean formation of the expected diastereomeric iminoboronate complexes is seen after ten minutes and once the excess base is filtered from the reaction mixture, these complexes are configurationally stable. For example, a ^{1}H NMR spectrum acquired after 24 hours revealed that no epimerisation has occurred (entry 5, Table 6). This confirms that potassium carbonate is an improved alternative to caesium carbonate when the amine to be derivatized contains a relatively acidic α-proton.

2.4 Conclusions

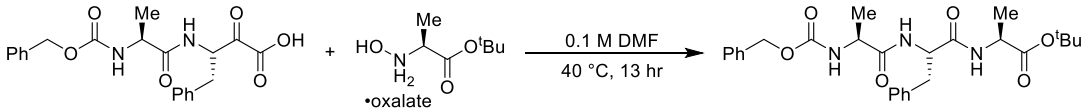
In summary, a three-component Strecker reaction for the asymmetric synthesis of α-arylglycines has been developed employing (*S*)-1-(4-methoxyphenyl)ethanamine as a chiral auxiliary. This three-component protocol involves the addition of arylaldehydes to a solution of (*S*)-1-(4-methoxyphenyl)ethanamine and sodium cyanide, with the resultant crystalline diastereomerically pure α-amino nitriles treated with 6M aqueous hydrochloric acid to yield the corresponding α-arylglycines. The enantiomeric excess of these α-arylglycines was determined by derivatization with 2-formylphenylboronic acid and (*S*)-BINOL followed by ^{1}H NMR spectroscopic analysis of the resultant mixtures of diastereomeric iminoboronate esters. Potential problems arising from epimerisation of the α-centre of the α-arylglycines has been addressed by employing the less soluble base potassium carbonate in place of caesium carbonate in the derivatization protocol. Results showed that simple filtration of the base after a reaction time of 10 minutes completely eliminates any epimerisation from occurring.[14]

3 A Simple Protocol for NMR Analysis of the Enantiomeric Purity of Chiral Hydroxylamines

The Bull-James group has so far published chiral derivatization protocols for determining the enantiomeric excess of chiral amines,[93,94] diols,[95,96,107] diamines,[105] amino alcohols[106] and α-arylglycines.[14] Hydroxylamines are important chiral molecules particularly in biochemistry, this chapter will discuss the development of simple methodology for their synthesis from their parent chiral amines and the development of the first derivatization protocol for determining their enantiopurity.

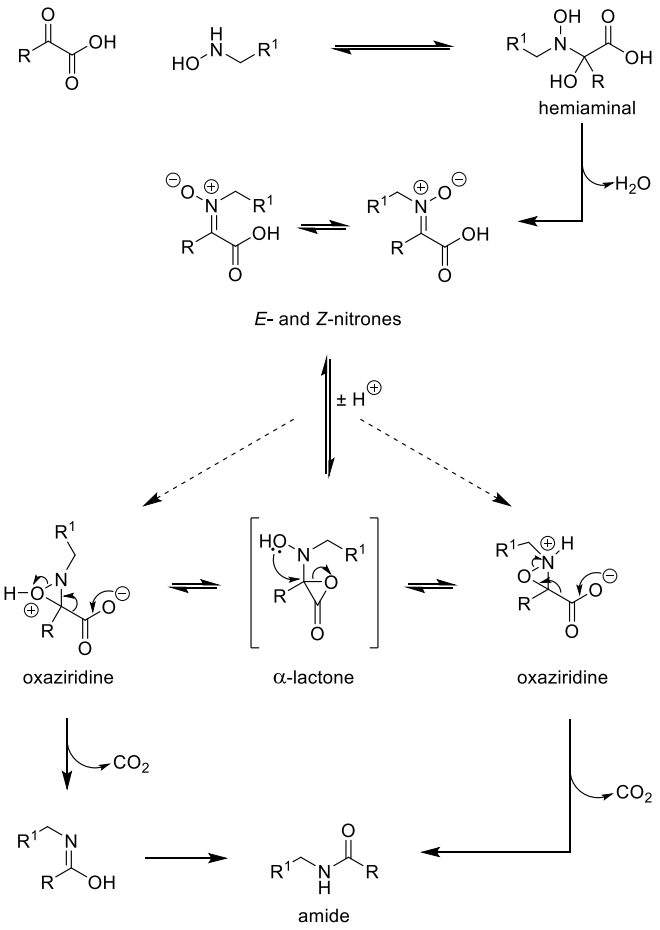
3.1 Introduction

Chiral hydroxylamines and their derivatives exhibit a wide range of biological properties,[125-128] and have been used as substrates for a wide range of synthetic methodologies. This includes reaction with α-keto-acids to afford amide bonds, with Bode recently reporting that chemoselective amide ligations were possible by simply warming the two reagents in dimethylformamide, without the need for additional reagents or catalysts (Scheme 65).[129]



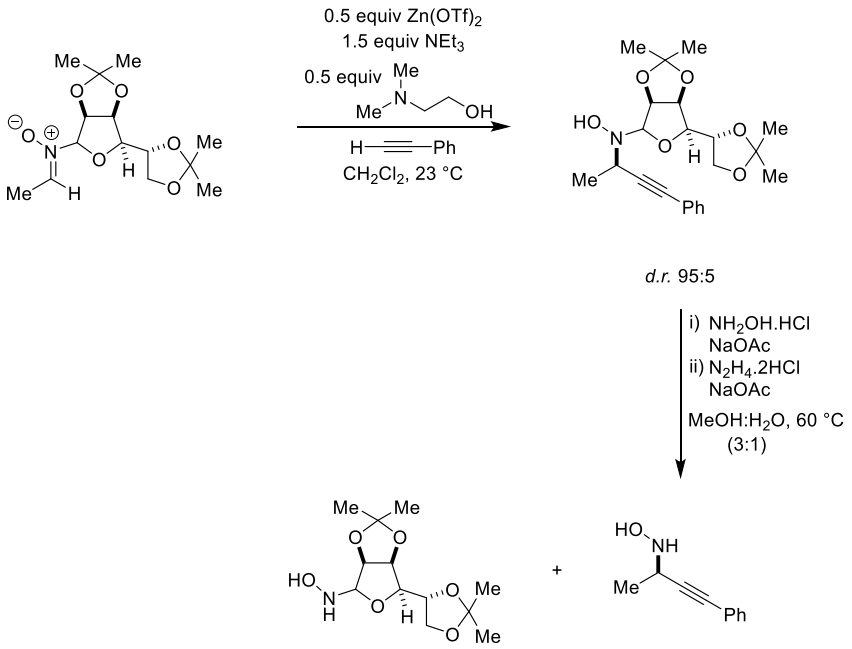
Scheme 65 – α-Ketoacid-hydroxylamine amide ligation

In 2012, Bode reported the mechanism for these types of ketoacid-hydroxylamine amide forming ligation reactions involving the formation of an intermediate nitrone and α-lactone (Scheme 66).[130]



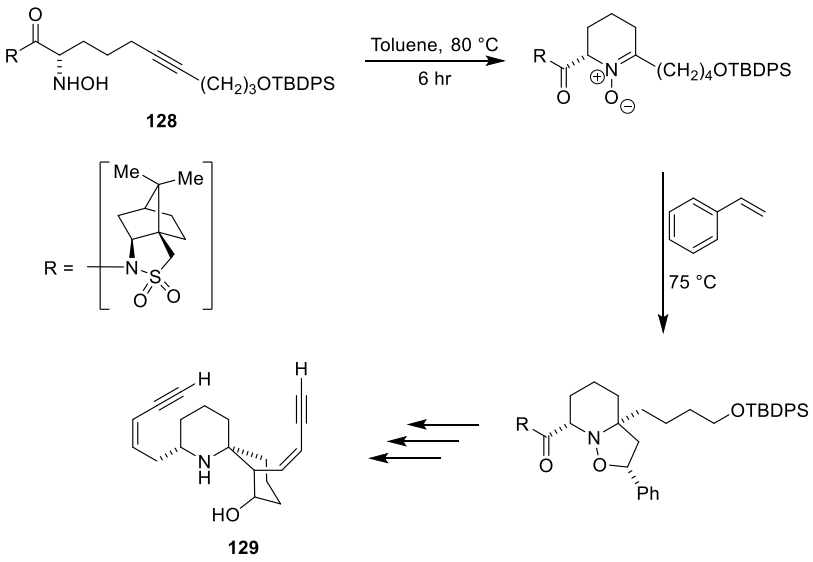
Scheme 66 - Proposed mechanism for α-ketoacid-hydroxylamine amide ligation

Their use as reagents for the asymmetric α-oxyacylation of cyclic ketones,[131] as substrates for the preparation of chiral Weinreb amide derivatives[132] and their condensation with aldehydes to afford chiral nitrones as substrates for asymmetric reactions have also been extensively reported.[133-138] In 2002, Carreira *et al.* published the first synthesis of optically pure propargylic *N*-hydroxylamines from chiral nitrones which employed a mannose-derived chiral auxiliary (Scheme 67).[136]



Scheme 67 - Asymmetric synthesis of propargylic *N*-hydroxylamines from nitrones

Hydroxylamines have also been employed as versatile chiral building blocks for the preparation of chiral hydroxamic acids,[139,140] β-amino acids,[141,142] peptides[143] and a number of natural products.[144-147] In 1999, Holmes *et al.* published the synthesis of Histrionicotoxin **129** which employed a chiral hydroxylamine intermediate **128** as a substrate for a key 1,3-dipolar cycloaddition reaction (Scheme 68).[145]



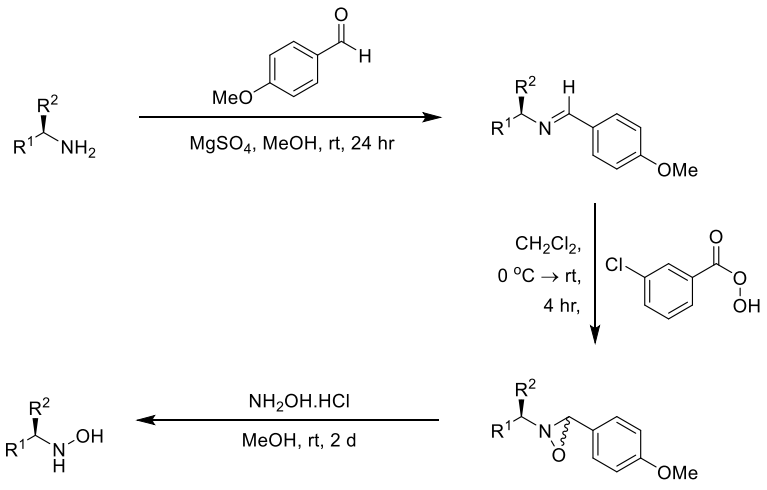
Scheme 68 - Synthesis of Histrionicotoxin 129 starting from hydroxylamine 128

Hydroxylamines are normally prepared *via* oxidation of a parent chiral amine,[148-152] stereoselective reduction of the corresponding oxime,[153] or *via* amination of chiral enolates.[154] Therefore, the development of a simple, rapid and inexpensive chiral derivatization protocol to enable the enantiomeric excess of chiral hydroxylamines to be determined by NMR spectroscopic analysis would be of great interest to the wider synthetic community.

3.2 Results and Discussion

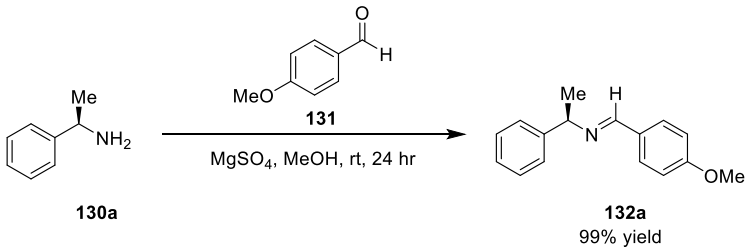
3.2.1 Synthesis of Chiral Hydroxylamines

As discussed above chiral hydroxylamines can be prepared in a number of different ways. [148-154] For our purposes, chiral hydroxylamines were synthesised from their parent chiral amines by adaptation of the literature procedure of Wovkulich and Uskoković, using a three-step protocol that had been reported to proceed with no racemisation (Scheme 69).[133]

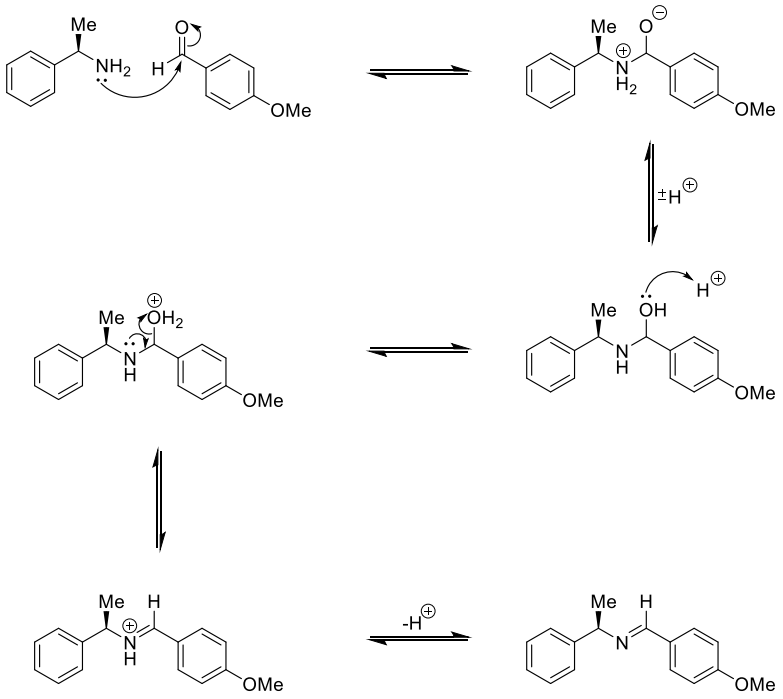


Scheme 69 - General synthesis of chiral hydroxylamines

Initially, it was decided to optimise this methodology using (*R*)-α-methylbenzylamine as a model substrate. Therefore, (*R*)-α-methylbenzylamine **130a** was converted to its corresponding imine **132a** in quantitative yield by addition of *p*-anisaldehyde **131**. The optimum conditions, to give the highest conversions for imine formation were found to be using methanol (MeOH) as solvent and magnesium sulphate ($MgSO_4$) as a drying agent to drive the reaction towards complete imine formation after 24 hours (Scheme 70). The well-established mechanism for imine formation in this reaction is shown in Scheme 71.[155]

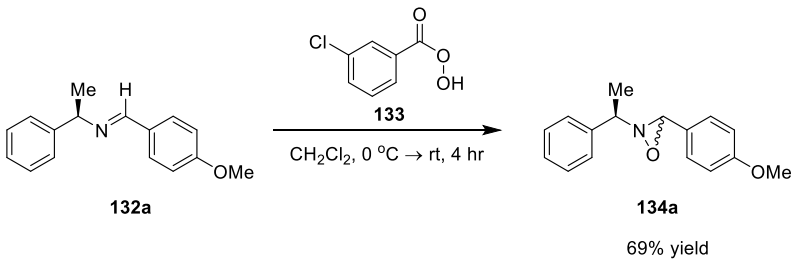


Scheme 70 – The reaction between (*R*)-α-methylbenzylamine 130a and *p*-anisaldehyde 131 to form imine 132a

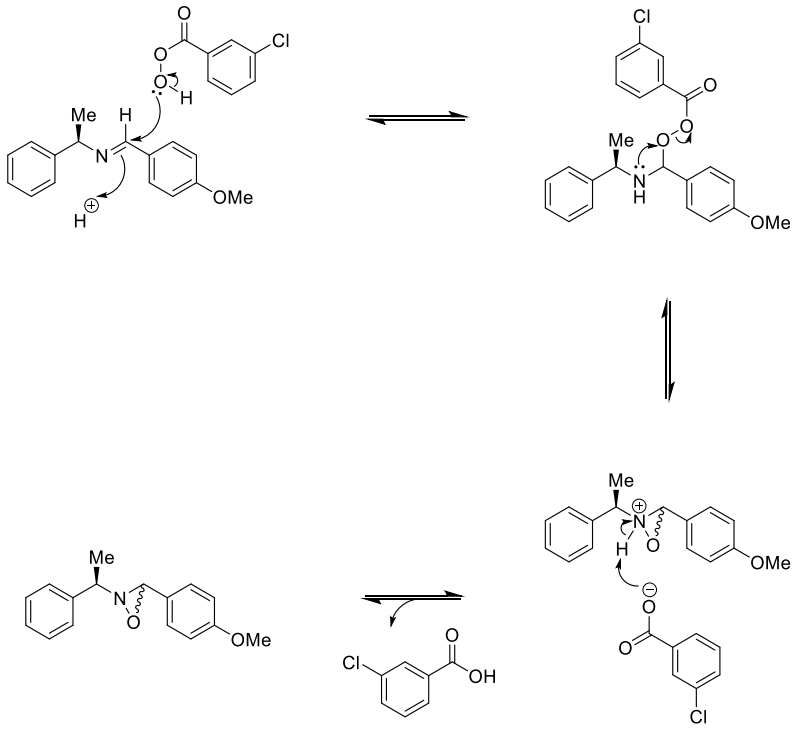


Scheme 71 - Mechanism of imine formation from (*R*)-α-methylbenzylamine 130a and *p*-anisaldehyde 131

The resultant imine **132a** was then oxidised with *meta*-chloroperoxybenzoic acid **133** (*m*CPBA) in dichloromethane (CH_2Cl_2) at 0 °C to give oxaziridine **134a** in 69% yield (Scheme 72). It was found that the yield of the oxidation reaction could be improved by first drying a solution of *m*CPBA in CH_2Cl_2 with $MgSO_4$ and using anhydrous CH_2Cl_2 as solvent.[153,154] Presumably, the presence of $MgSO_4$ removes water from the reaction mixture, thus preventing unwanted hydrolysis of the imine substrate back to its parent aldehyde. A reasonable mechanism for the formation of oxaziridine **134a** is shown in Scheme 73.

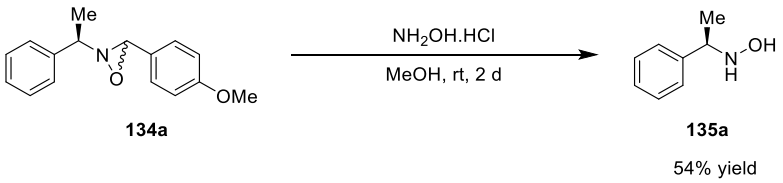


Scheme 72 - Oxidation of imine 132a to oxaziridine 134a using *m*CPBA 133



Scheme 73 – Mechanism of the oxidation of an imine to an oxaziridine

The crude oxaziridine **134a** was then transformed into its corresponding hydroxylamine *via* treatment with hydroxylamine hydrochloride in methanol to afford (*R*)-*N*-(1-phenylethyl) hydroxylamine **135a** in 54% yield (Scheme 74).



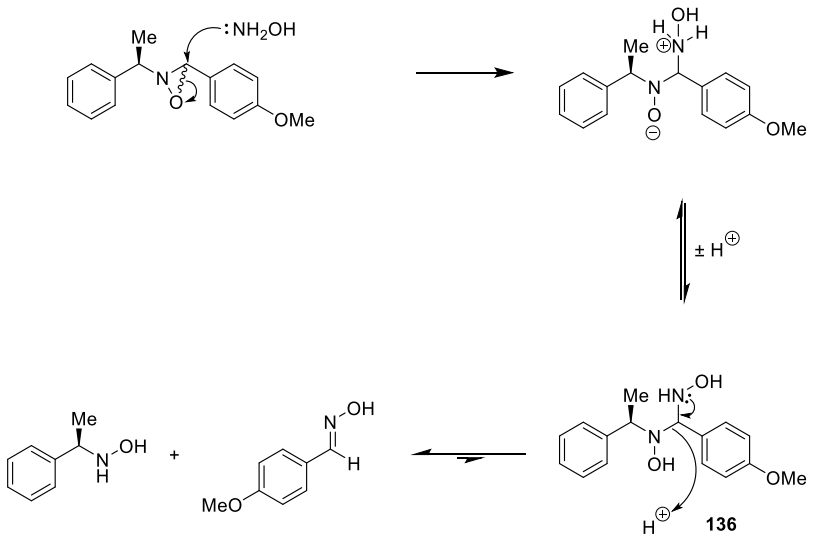
134a **135a**

54% yield

Scheme 74 – Conversion of oxaziridine 134a into hydroxylamine 135a

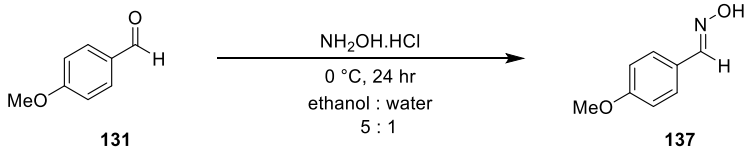
This final step produces the hydroxylamine as its hydrochloride salt, with the free hydroxylamine then being precipitated in its pure form from the aqueous layer using a basic workup (sodium bicarbonate).

The mechanism for the conversion of the oxaziridine **134a** to its corresponding hydroxylamine **135a** had not, to date, been discussed in the literature. In order to propose a mechanism for this step in the synthesis route, the composition of the aqueous washings after the basic workup was inspected using ^{1}H NMR spectroscopy to determine what by-product had been formed from cleavage of the *para*-methoxybenzyl fragment. We postulated that the hydroxylamine hydrochloride was likely to attack the oxaziridine ring at its benzylic position to afford a *bis*-hydroxylamine intermediate **136** that then fragments to afford desired hydroxylamine **135a** and the oxime of *p*-anisaldehyde **131** (Scheme 75).



Scheme 75 - Proposed mechanism for the conversion of an oxaziridine into a hydroxylamine

In order to confirm this hypothesis, the appropriate oxime **137** was prepared independently by addition of hydroxylamine hydrochloride to *p*-anisaldehyde **131** in a 5:1 ethanol:water mixture (Scheme 76).

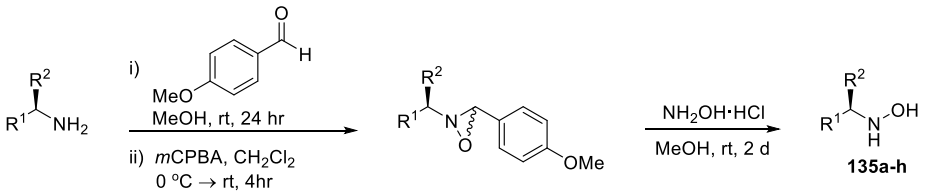


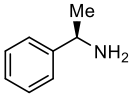
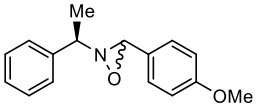
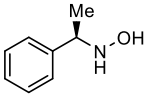
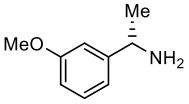
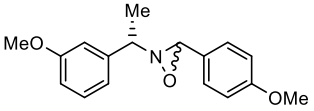
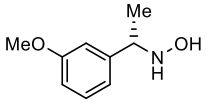
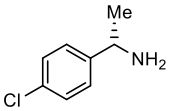
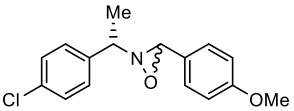
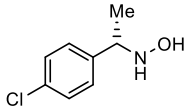
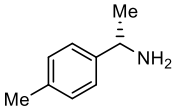
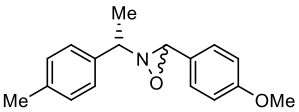
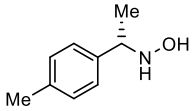
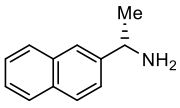
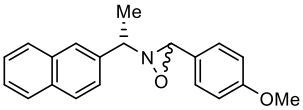
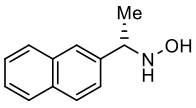
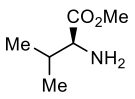
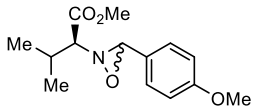
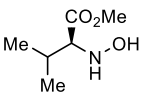
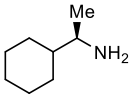
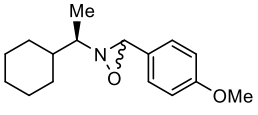
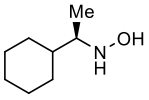
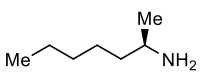
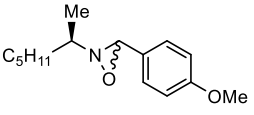
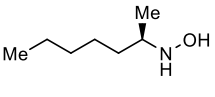
Scheme 76 – Synthesis of oxime 137

The presence of this oxime **137** as a by-product of the hydroxylamine reaction was confirmed in the residue obtained from the aqueous washings by comparison of its mass spectroscopic and ^{1}H NMR spectroscopic data with that of the independently synthesised oxime. The confirmation of the formation of an oxime species as a by-product of hydroxylamine formation gives credence to our proposed mechanism for the conversion of oxaziridine **134a** to hydroxylamine **135a**.

This method was then repeated using a number of commercially available primary amines in order to synthesise the range of chiral hydroxylamines **135a-h** shown in Table 7.

Table 7 – Synthesis of a range of chiral hydroxylamines from their parent amines

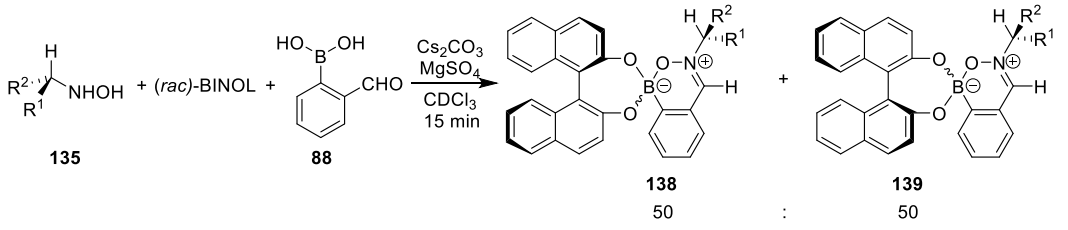


entry	amine	oxaziridine	hydroxylamine **135**
a		 **69 %**	 **135a 54 %, *e.e.* = 99 %**
b		 **71 %**	 **135b 55 %, *e.e.* = 99 %**
c		 **70 %**	 **135c 62 %, *e.e.* = 99 %**
d		 **56 %**	 **135d 38 %, *e.e.* = 99 %**
e		 **60 %**	 **135e 32 %, *e.e.* = 99 %**
f		 **68 %**	 **135f 46 %, *e.e.* = 99 %**
g		 **75 %**	 **135g 65 %, *e.e.* = 99 %**
h		 **52 %**	 **135h 32 %, *e.e.* = 99 %**

Hydroxylamines **135a-h** were synthesised in moderate to good yields from their parent amines with their structures confirmed by the presence of a broad OH stretch in their IR spectrum, mass spectrometry and ^{1}H and ^{13}C spectroscopic analysis. The data obtained for **135a**,[156] **135e**[152] and **135f**[157] agreed with previously reported data, however, characterisation data was not available in the literature for hydroxylamines **135b, 135c, 135d, 135g** and **135h** and is reported herein. Substitution of the aryl ring in analogues **135a-e** was generally well tolerated with a small effect on the yield for the tolyl and naphthyl hydroxylamines **135d** and **135e,** whilst the conversion of amino **135f** was also shown to proceed in good yield.

3.2.2 Development of a Protocol to Determine the Enantiomeric Excess of Chiral Hydroxylamines

As described, our group have previously reported the development of chiral derivatization protocols for determining the *e.e.* of chiral primary amines,[93,94] diamines,[105] amino alcohols[106] and diols.[95,96] Consequently, we decided to develop a three component coupling protocol to accurately determine the enantiomeric excesses of our chiral hydroxylamines. Initially, 1.0 equivalent of (*R*)-*N*-(1-phenylethyl) hydroxylamine **135a** was treated with 1.0 equivalent of 2-formylphenylboronic acid **88**, 1.1 equivalents of (*rac*)-BINOL and 1.1 equivalents of caesium carbonate (Cs_2CO_3) in $CDCl_3$ in the presence of $MgSO_4$ and the resultant reaction mixture stirred for 15 minutes.



Scheme 77 – Three component NMR protocol for determining the enantiomeric excess of chiral hydroxylamines

The reaction mixture was then filtered and a ^{1}H NMR spectrum acquired, which revealed the clean formation of a 50:50 mixture of diastereomeric nitrono-boronate ester complexes (*R*,*R*)-**138a** and (*R*,*S*)-**139a** in a quantitative yield, with baseline resolution observed for the benzylic and methyl protons of each diastereomer respectively. This meant that the relative intensities of the two different sets of diastereomeric integrals could potentially be compared to accurately determine the enantiopurity of a scalemic sample of the parent hydroxylamine by ^{1}H NMR spectroscopy (Figure 34).

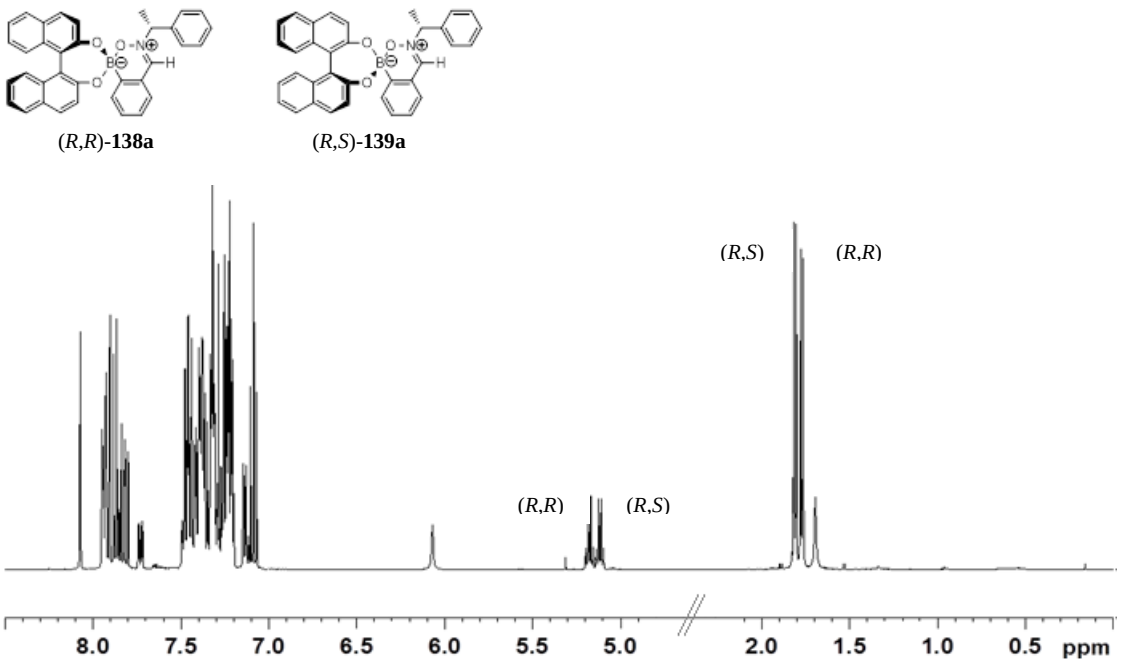
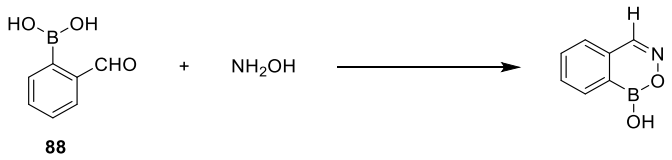


Figure 34 - ^{1}H NMR spectrum of nitrono-boronate diastereomers 138a and 139a

^{11}B NMR spectroscopic analysis of the resultant mixture of diastereomeric complexes formed by derivatization of hydroxylamine **135a** showed a single resonance at 11.8 ppm for the boronate environment and ^{1}H NMR spectroscopic analysis revealed the diastereomeric imine resonances to be at 7.93 ppm and 8.23 ppm. The comparable resonances for the diastereomeric iminoboronate complexes formed from derivatization of (*R*)-α-methylbenzylamine (the parent amine of

hydroxylamine **135a**) are at 14.0 ppm in the ^{11}B NMR spectrum for the boronate environment and 8.16 ppm and 8.33 ppm for the imine resonances in the ^{1}H NMR spectrum. These subtle downshifts in the ^{11}B and ^{1}H NMR spectra indicated to us that nitrono-boronate structures were formed in the derivatization reactions with coordination of the hydroxylamine oxygen to the boron atom.

The structure of these nitrono-boronate complexes was then confirmed by X-ray crystallographic analysis (*vide infra*). This class of compound has not been extensively reported in the literature,[158,159] with the only report by Dewar[160-163] and Snyder[164-168] in the 1960's *via* the reaction of 2-formylphenylboronic acid **88** and hydroxylamine (Scheme 78).



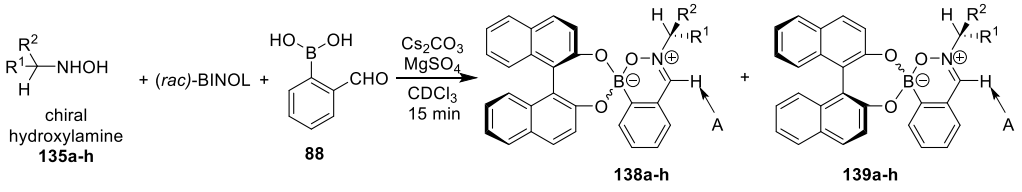
Scheme 78 - First reported synthesis of a nitrono-boronate compound[164]

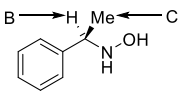
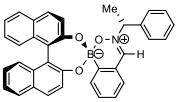
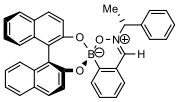
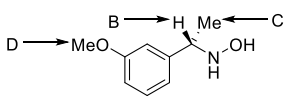
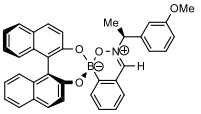
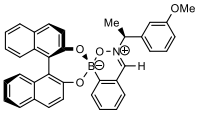
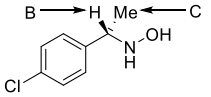
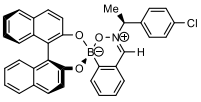
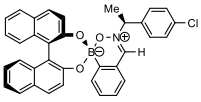
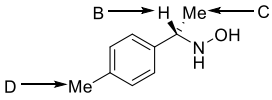
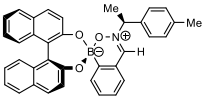
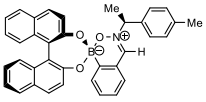
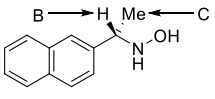
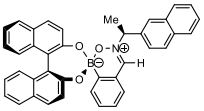
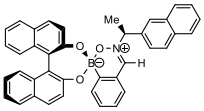
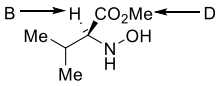
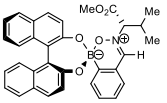
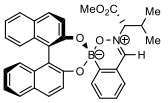
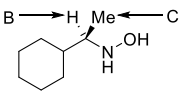
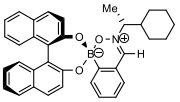
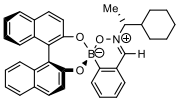
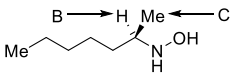
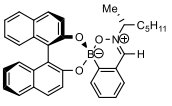
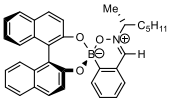
To investigate the scope and limitations of this chiral derivatization protocol further, the remaining hydroxylamines **135b-h** were then derivatized under the same conditions. Analysis of the 500 MHz ^{1}H NMR spectra of the resultant nitrono-boronate esters **138b-h/139b-h** revealed baseline resolution of at least two sets of resonances had occurred in all cases. For example, analysis of the 500 MHz ^{1}H NMR spectrum of a 50:50 mixture of nitrono-boronate esters **138e** and **139e** revealed that baseline resolution had occurred for three distinct sets of resonances with the largest $\Delta\delta$ value of 0.193 ppm being observed for their imine protons. In all cases splitting of the α-protons and methyl protons of the hydroxylamine fragments of **138a-h/139a-h** were observed. Contrary to the previously reported protocols by the Bull-James group using iminoboronate complexes,[93,95] baseline resolution of the imine protons of complexes **138a-h**/**139a-h**was not achieved in all cases. This was

because they were obscured by aromatic resonances, although baseline resolution of the imine protons of the complexes **138a-h**/**139a-h** was observed.

The individual resonances of each pair of diastereomers were assigned by comparison with the ^{1}H NMR spectra of authentic samples of diastereomerically pure **138a-h** and **139a-h** that were prepared independently *via* separate reaction of enantiopure hydroxylamines **135a-h** with (*R*)-BINOL and (*S*)-BINOL respectively. The $\Delta\delta$ differences in the chemical shifts observed for each pair of diastereomeric nitrono-boronate esters are reported in Table 8. Independent preparation of **138a-h** and **139a-h** from reaction of hydroxylamines **135a-h** with (*R*)-BINOL and (*S*)-BINOL respectively also demonstrated to us that the synthetic protocol for converting an enantiopure amine into a hydroxylamine *via* an oxaziridine proceeded with full retention of stereochemistry and thus yielded enantiopure hydroxylamines in all cases since, using the example of the preparation of **138a**, only a single quartet at 5.15 ppm and single doublet at 1.75 ppm were seen in the resultant 500 MHz ^{1}H NMR spectrum after derivatization. Had loss of stereochemistry occurred during this synthetic protocol to yield hydroxylamine **135a** then the ^{1}H NMR spectrum of **138a** would have contained diastereomeric resonances, such as those seen in Figure 34, whose integrals would have corresponded to the enantiopurity of the hydroxylamine.

Table 8 - Chemical Shift Differences in the 500 MHz ^{1}H NMR Spectra of 50:50 Mixtures of Diastereomers 138a-h and 139a-h Derived from Hydroxylamines 135a-h



entry	hydroxylamine **1**	nitrono-boronate esters **138**/**139**[a]		Δδ (δ**138** - δ**139**) (ppm)[b]
1	 (*R*)-**135a**	 (*R*,*R*)-**138a**	 (*R*,*S*)-**139a**	0.059 (B) -0.039 (C)
2	 (*S*)-**135b**	 (*S*,*S*)-**138b**	 (*S*,*R*)-**139b**	0.039 (B) -0.044 (C) -0.219 (D)
3	 (*S*)-**135c**	 (*S*,*S*)-**138c**	 (*S*,*R*)-**139c**	0.101 (B) -0.010 (C)
4	 (*S*)-**135d**	 (*S*,*S*)-**138d**	 (*S*,*R*)-**139d**	0.054 (B) -0.061 (C) -0.050 (D)
5	 (*S*)-**135e**	 (S,*S*)-**138e**	 (*S*,*R*)-**139e**	0.193 (A) 0.059 (B) -0.058 (C)
6	 (*S*)-**135f**	 (*S*,*S*)-**138f**	 (*S*,*R*)-**139f**	0.013 (A) 0.018 (B) 0.080 (D)
7	 (*R*)-**135g**	 (*R*,*R*)-**138g**	 (*R*,*S*)-**139g**	0.101 (B) 0.107 (C)
8	 (*R*)-**135h**	 (*R*,*R*)-**138h**	 (*R*,*S*)-**139h**	0.116 (A)[c] -0.235 (B) -0.242 (C)

[a] Diastereomer **138** corresponds to homochiral (*R*,*R*) or (*S*,*S*)-complex, and diastereomer **139**corresponds to heterochiral (*R*,*S*) or (*S*,*R*) complex. [b] A negative value for Δδ indicates that the resonance corresponding to the heterochiral diastereomer **139** is more deshielded than that of the homochiral diastereomer **138**. [c] Δδ calculated for imine carbon resonances of ^{13}C NMR spectrum of **138h**/**139h**.

The resonances of the α-protons of the heterochiral diastereomers **139a-h** were found to be shielded relative to the resonances for their corresponding homochiral diastereomers **138a-h**. Conversely, the resonances of the α-methyl protons of the heterochiral diastereomers **139a-h** were deshielded relative to the resonances of their corresponding homochiral diastereomers **138a-h**. Therefore, consideration of the sign of the Δδ value could potentially be used to assign the unknown configuration of chiral α-methyl, α-aryl hydroxylamines formed in asymmetric protocols.

The detection limit of this protocol was determined *via* derivatization of three samples of (*rac*)-BINOL of 98%, 80% and 0% with enantiopure hydroxylamine **135b** and 2-formylphenylboronic acid. Scalemic samples of BINOL and enantiopure hydroxylamine were used in this study for experimental convenience. However, it follows that use of enantiopure BINOL would enable the enantiopurity of a scalemic sample of hydroxylamine **135b** to be determined.

Analysis of the ^{1}H NMR spectrum of each sample revealed that the calculated diastereomeric ratio of the resultant mixture of (*S*,*S*)-**138b** and (*S*,*R*)-**139b** were in good agreement with the known enantiopurity of the starting hydroxylamine **135b** (Figure 35).

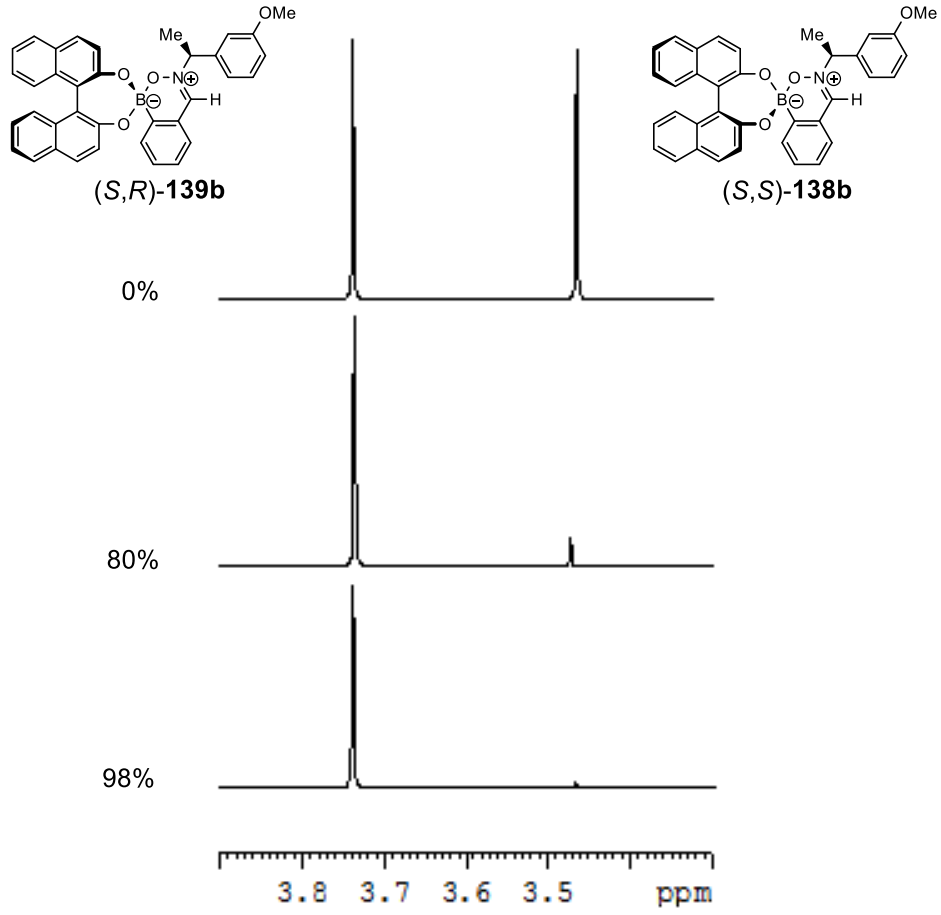


Figure 35 - Expansion of the methoxy region of the ^{1}H NMR spectra of mixtures of complexes 138b and 139b prepared from hydroxylamine (*S*)-135b, 2-formylphenylboronic acid 88 and samples or (*R*)-BINOL of 0%, 80% and 98% *e.e.*

For example, the integrals measured from the ^{1}H NMR spectra of mixtures for the methoxy groups of (*S*,*S*)-**138b** and (*S*,*R*)-**139b** of 98%, 79% and 0% *dr* were in excellent agreement with the known enantiopurity of the starting BINOL of 98%, 80% and 0% *e.e.* respectively, indicating that no kinetic resolution had occurred during derivatization. These values are well within the 5% error limit normally accepted for CDA analysis using NMR spectroscopy,[169,170] demonstrating that this derivatization protocol is a highly effective, cheap and fast method for determining the *e.e.* of hydroxylamines.

Application of this derivatization protocol to hydroxylamine **135h** proved problematic, because the α-protons of its diastereomeric nitrono-boronate esters

138h and **139h** were not baseline resolved in its ^{1}H NMR spectrum, whilst its α-methyl protons were obscured by resonances from its alkyl backbone. This meant that no pairs of diastereomeric resonances were baseline resolved, thus preventing the enantiopurity of the parent hydroxylamine **135h** from being determined by ^{1}H NMR spectroscopy. However, inspection of the ^{13}C NMR spectrum of a 50:50 mixture of nitrono-boronate esters **138h** and **139h** revealed that baseline splitting had occurred for all of the diastereomeric resonances (Figure 36).

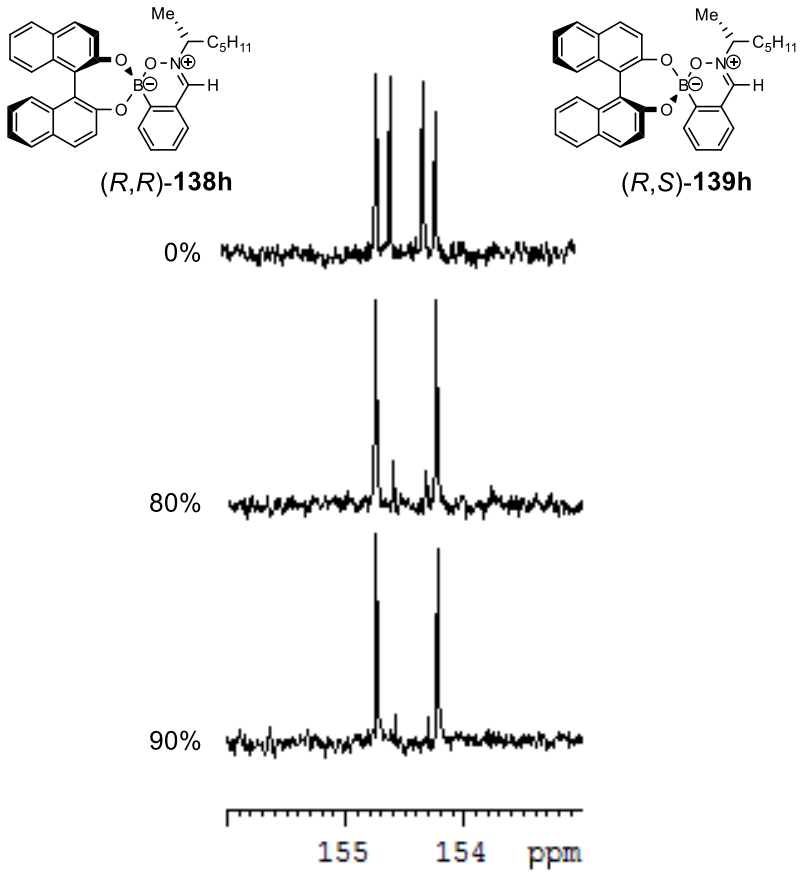
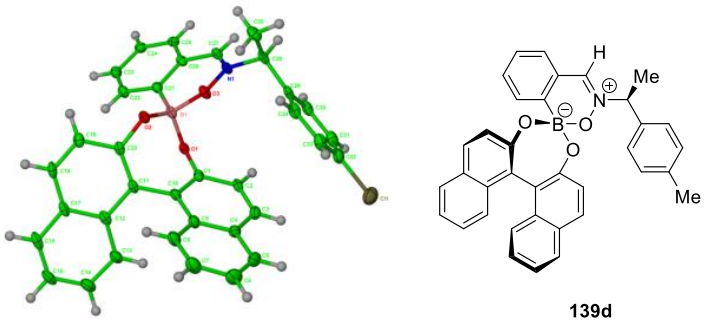


Figure 36 - Expansion of the ^{13}C NMR spectrum of the imine proton of a mixture of 138h and 139h prepared from (*R*)-135h, 2-formylphenylboronic acid 88 and (*R*)-BINOL of 0%, 80% and 90% *e.e.*

In order to enable accurate integration of the peak areas of pairs of diastereomeric resonances of nitrono-boronates **138h**/**139h** these ^{13}C NMR experiments were carried out using a d1 delay between pulses of 120 seconds which allows T1 relaxation to recover fully (the T1 relaxation is the measurement of how quickly the net magnetisation vector recovers to its thermodynamic equilibrium in the direction of the magnetic field B_o). The experiments were also performed using an inverse-gated decoupling pulse sequence, this turns off the ^{1}H decoupler during the 120 second recycle delay which stops any NOE build-up (the transfer of nuclear spin polarization from one nuclear spin population to another *via* cross relaxation) which can enhance the ^{13}C signals in a non-uniform manner.

As before, samples of BINOL of 90%, 80% and 0% *e.e.* were derivatized using enantiopure (*R*)-**135h** and 2-formylphenylboronic acid. Measurement of the integrals of the ^{13}C NMR spectrum of these mixtures of (*R*,*R*)-**138h** and (*R*,*S*)-**139h** revealed *d.r.*s of 91%, 82% and 0% which were in excellent agreement with the known enantiopurity of the starting BINOL.

X-ray crystallographic analysis of diastereomer (*S*,*R*)-**139d** prepared from (*S*)-hydroxylamine **135d** and enantiopure (*R*)-BINOL and recrystallized from deuterated chloroform showed that its nitrono-boronate structure was clearly different to the 5-membered iminoboronate ester reported previously for derivatization of amines using this protocol (Figure 37).[93,95]



139d

Figure 37 – X-ray crystal structure of nitrono-boronate ester (*S*,*R*)-139d

Nitrono-boronate ester (*S*,*R*)-**139d** has a tetrahedral sp^3 boron atom whose presence in solution was also confirmed by ^{11}B NMR spectroscopic analysis which revealed a single resonance visible at δ12.0 ppm. However, in contrast to the iminoboronate structures reported previously, its 6-membered ring contains an unusual zwitterionic N^+-O-B^- arrangement. Further inspection of the crystal structure reveals that its 6-membered ring is comprised of coplanar carbon, nitrogen and oxygen atoms with its spirocyclic boron atom occupying the bow position of a half-chair conformer.

3.3 Conclusions

In conclusion, a range of chiral hydroxylamines have been synthesised and the first known chiral derivatization protocol for determining the enantiopurity of chiral hydroxylamines by NMR spectroscopy has been developed.[171] The range and scope of this protocol has been investigated by successfully applying it to a range of chiral hydroxylamines, with scalemic sampling proving its accuracy. ^1H NMR spectroscopy has been shown as a quick and effective tool for the determination of enantiomeric excess and where this is not possible ^{13}C NMR spectroscopy has been shown as an accurate alternative. Finally, a mechanism has been proposed for the conversion of an oxaziridine intermediate into the product hydroxylamine, which was confirmed by isolation of an oxime by-product formed during the synthesis.

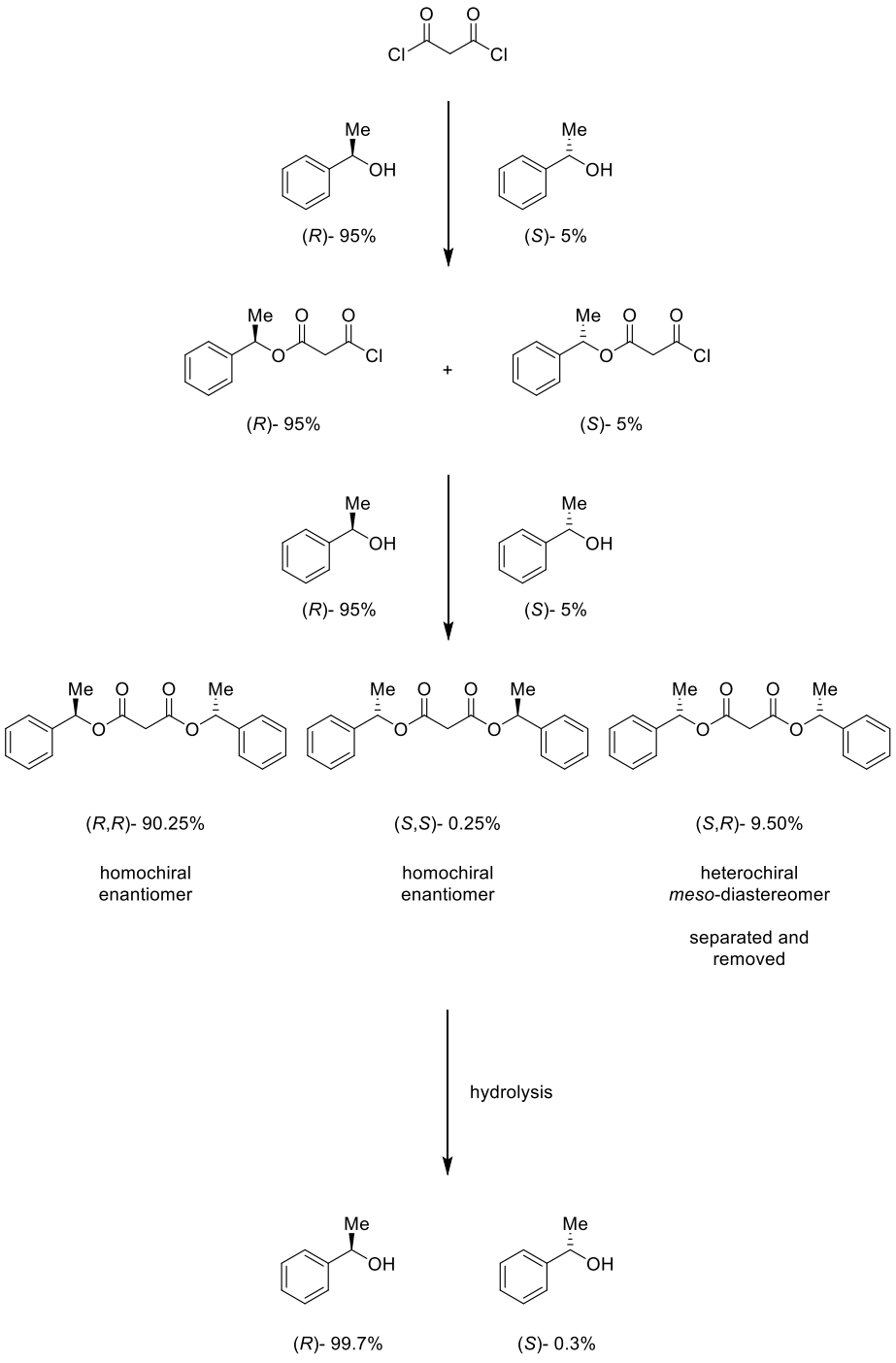
4 A Simple Protocol for NMR Analysis of the Enantiomeric Purity of Chiral Diols Using an Achiral Diboronic Acid Template

4.1 Introduction

The following chapter details our investigation into the development of a new derivatization protocol for determining the enantiomeric excess of chiral diols. Our aim was to employ a bifunctional, achiral template as a derivatization agent to yield a series of heterochiral and homochiral diastereomers from which enantiomeric excess could be determined by ^{1}H NMR spectroscopic analysis.

4.1.1 The Horeau Principle

First discovered in the late 1960's "The Horeau Principle" involves the formation of a series of homochiral and heterochiral diastereomers from a bifunctional achiral auxiliary and two equivalents of a chiral substrate.[172-174] The application of this principle was first reported by Horeau for the enhancement of optical purity through duplication.[173] Using an example of the reaction between malonyl chloride and two equivalents of scalemic 1-phenylethanol to form a series of diastereomeric malonates, Horeau demonstrated how material of 90% enantiomeric excess could be enhanced to an enantiomeric excess of 99.4% in a single duplication (Scheme 79).



Scheme 79 – A single Horeau duplication to enhance (*R*)-1-phenylethanol from 90% *e.e.* to 99.4% *e.e.*

If no chiral recognition occurs and diastereomer formation is statistical then one equivalent of 1-phenylethanol will react with one equivalent of malonyl chloride to form the mono-substituted products in the same ratio as the enantiomeric ratio of the

1-phenylethanol. For the second addition of 1-phenylethanol to form the diastereomeric dimers the statistical addition will form products in the following ratios: the mono-substituted (*R*) enantiomer (95%) will react with the scalemic 1-phenylethanol to give 90.25% of the (*R*,*R*) diastereomer (0.95 x 0.95 = 0.9025) and 4.75% of the (*R*,*S*)-*meso*-diastereomer (0.95 x 0.05 = 0.0475). Additionally, the mono-substituted (*S*) enantiomer (5%) will react with the scalemic 1-phenylethanol to give 0.25% of the (*S*,*S*) diastereomer (0.05 x 0.05 = 0.0025) and 4.75% of the (*S*,*R*)-*meso*-diastereomer (0.05 x 0.95 = 0.0475). Of these four diastereomers, the (*R*,*R*) and (*S*,*S*) diastereomers make up an enantiomeric pair and the (*R*,*S*) diastereomer and its apparent (*S*,*R*) "enantiomer" are actually identical and are the *meso* compound. Thus, after removal of the *meso* compound from the mixture of diastereomeric products, the enantiomeric pair are present in a 90.25:0.25 ratio which when normalised amounts to an enantiomeric ratio of 99.7:0.3 (99.4% enantiomeric excess). This process removes the minor (*S*)-1-phenylethanol enantiomer through incorporation into the *meso* compound which can potentially be separated. Therefore if hydrolysis of the homochiral diester product proceeds with retention of the 99.7:0.3 stereochemical ratio then the (*R*)-1-phenylethanol is isolated in an enantiomeric excess which has been enhanced from 90% to 99.4%. Horeau also proposed that sequential use of this method could enhance chiral material of 30% enantiomeric excess to 98.6% over three rounds. However, the disadvantage to this procedure is that there is a loss in yield when separating out the *meso* compound, and as the enantiomeric ratio of the chiral substrate tends towards racemic, the greater the amount of material will be lost to the *meso* compound. Sequential duplications will compound the effect further, but as rigorously chirally purified substrates are highly desirable to asymmetric synthetic protocols a loss in yield can become acceptable if it results in isolation of an essentially enantiopure chiral substrate.

Horeau's method is an example of a positive non-linear effect, a phenomenon which has been investigated extensively by Kagan and co-workers as applied to asymmetric amplification[175] and asymmetric catalysis.[176,177] In asymmetric catalysis, it is often accepted that the enantiomeric excess of the product is linearly correlated

to the enantiomeric excess of the chiral auxiliary employed, such that it obeys the relationship in Equation 1.

$$e.e._{max} = e.e._{product} / e.e._{auxiliary} \quad (1)$$

However, as noted by Kagan *et al*., this does not take into account potential interactions between dimeric catalytic species.[178] It was reported that for a system that forms diastereomeric catalytic complexes from two equivalents of chiral ligand (an ML_2 system), if the chiral ligand is not enantiopure then three different diastereomeric catalytic complexes will be formed: ML_RL_R, ML_SL_S and ML_RL_S, where ML_RL_S is the *meso* catalyst. The amounts of each of the three different complexes, if no chiral recognition occurs on formation, will be distributed as described above for the formation of diastereomers according to Horeau's duplication method. If the *meso* complex is less catalytically active than the homochiral enantiomeric catalysts then a positive non-linear effect is observed (curve B, Figure 38) whereby the enantiomeric excess of the product is higher than expected. Conversely, if the *meso* complex is more catalytically active than the homochiral catalyst, a negative non-linear effect is observed (curve C, Figure 38) whereby the enantiomeric excess of the product is less than expected as according to Equation 1.

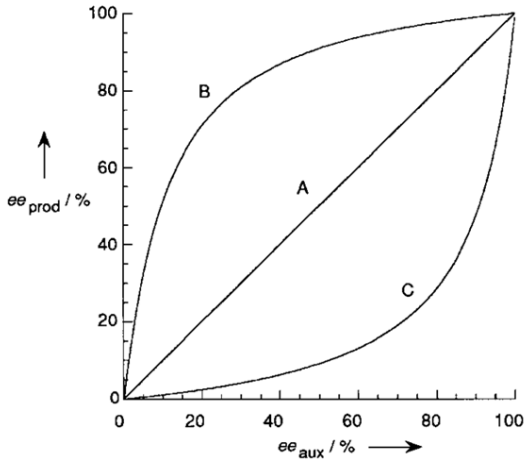
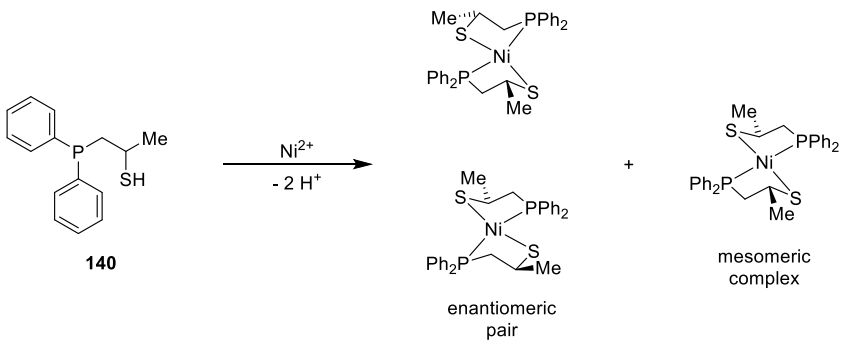


Figure 38 - Typical curves for positive (B) and negative (C) non-linear effects[176]

4.1.2 Enantiomeric Excess Determination by the Horeau Method

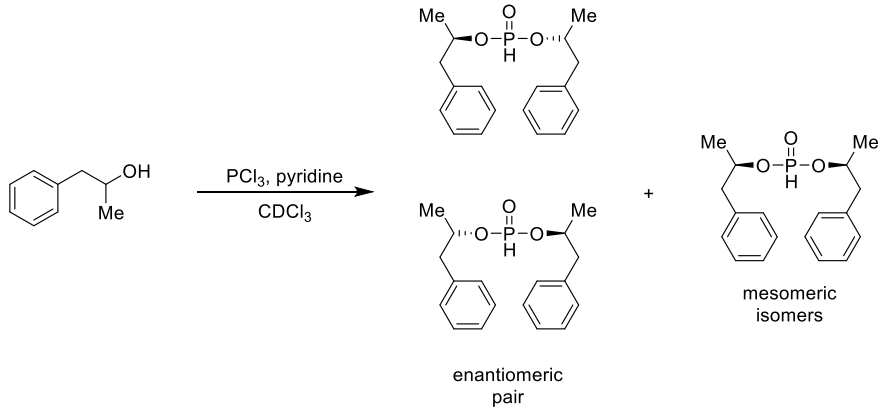
Over a decade after Horeau's work was published, a number of groups developed methodologies using his findings to determine enantiomeric excess of chiral molecules with NMR spectroscopy. The first of these published methodologies was in 1985 by Marty *et al.*, where the enantiomeric excess of 1-diphenylphosphino-2-propanethiol **140** was determined by ^{31}P and ^{1}H NMR spectroscopy *via* addition of $Ni(NO_3)_2 \cdot 6H_2O$ (Scheme 80).[179]



Scheme 80 – Diastereomeric nickel complexes for determining the enantiomeric excess of chiral thiols

Addition of $Ni(NO_3)_2 \cdot 6H_2O$ to thiol **140** led to formation of a diastereomeric series of *trans*-nickel complexes of which two were an enantiomeric pair and a *meso* complex. The *meso*:enantiomer ratio was then determined from integration of P and CH_3 resonances in the ^{31}P and ^{1}H NMR spectra of the resultant diastereomeric mixture and Marty reported that it was possible to determine enantiomeric excess to within 0.1% of the known values.

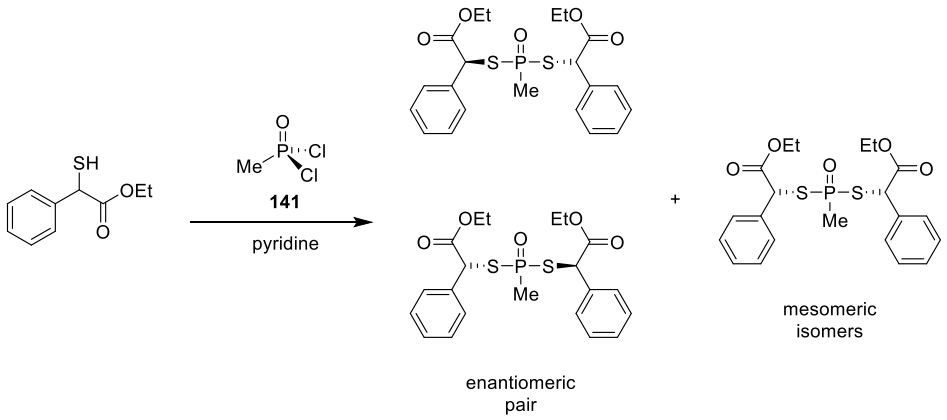
A large amount of the early research into this area was reported by Feringa *et al.* who developed protocols to determine the enantiomeric excess of chiral alcohols,[180,181] thiols,[181,182] amines[183] and amino esters[183] using ^{31}P NMR spectroscopy. Feringa's initial study showed that addition of PCl_3 to racemic alcohol produced a series of phosphonate diastereomers, two of which were an enantiomeric pair and the *meso* compound (Scheme 81).[180]



Scheme 81 - Diastereomeric phosphonate dimers formed from reaction of a racemic alcohol and PCl_3

The ^{31}P NMR spectra of the dimers formed from the addition of PCl_3 to a chiral alcohol showed that the *meso*:enantiomer ratio calculated from the corresponding resonance integrations gave excellent agreement to within 1% of the 50:50 enantiomeric ratios of the starting alcohol for a range of structurally diverse alcohols.

A further report by Feringa *et al.* attempted to use the same methodology for determining the enantiomeric excess of chiral thiols.[181] However, this was shown not to be possible and a new modified reagent was developed, with methylphosphonic dichloride **141** shown to be an effective reagent to form diastereomeric phosphonates from chiral thiols (Scheme 82).

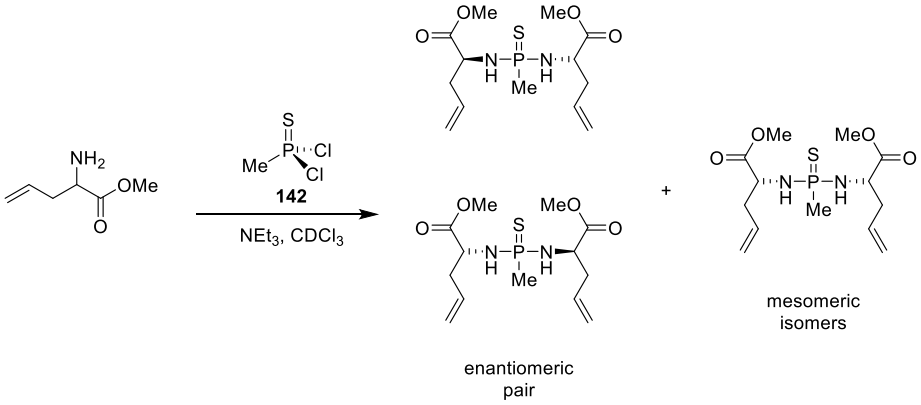


Scheme 82 - Methylphosphonic dichloride as a coupling reagent for chiral thiols

Once again the ratios obtained from ^{31}P NMR spectra showed excellent agreement with those expected for racemic thiols. This new methodology was also reported to be applicable to chiral alcohols, however, reaction times were longer than when using PCl_3 and chemical shift differences ($\Delta\delta$) were slightly reduced. Methylphosphonic dichloride **141** has a number of advantages over PCl_3 as it is a solid and thus easier to handle and can also be used with acid sensitive alcohols. This type of coupling reagent was further investigated in order to determine the optimum structure of the reagent by modifying the heteroatom (between O and S) and the length of the alkyl chain.[182] It was found that methylphosphonic dichloride **141** was the optimum coupling reagent as it gave the largest chemical shift differences between the enantiomeric pair and the corresponding *meso* diastereomer.

Feringa's research extended to developing a method for determining the enantiomeric excess of chiral amines and amino esters.[183] Methylphosphonothioic

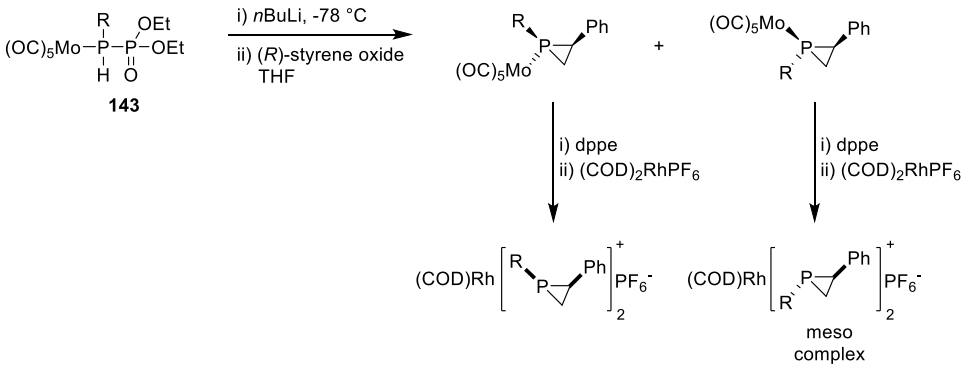
dichloride **142** was shown to be the reagent of choice since the previously reported PCl_3 and methylphosphonic dichloride **141** proved not to be effective coupling reagents for these types of compound (Scheme 83).



Scheme 83 - Methylphosphonothioic dichloride as a coupling reagent for amino esters

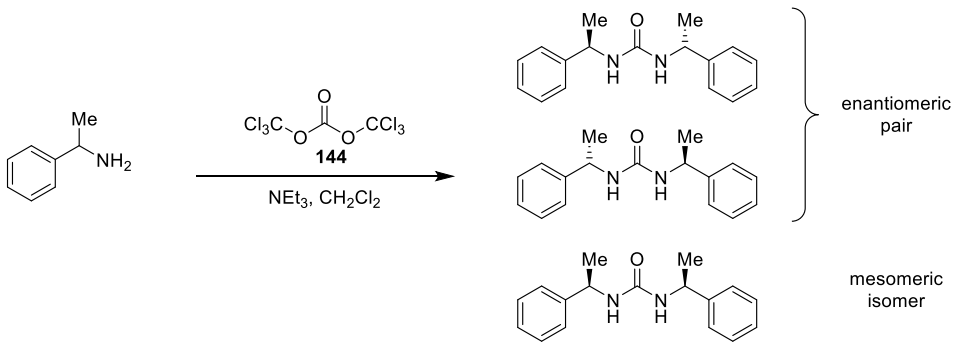
This methodology was demonstrated to proceed without racemization or kinetic resolution for the formation of the Horeau series of phosphonic diamide diastereomers. A number of optically active amines of known enantiomeric excess were successfully derivatized and integration of the relevant signals in the ^{31}P NMR spectra determined the enantiomeric excess of chiral amines to within 3% of true values.

In 1993, Marinetti *et al.* demonstrated a method for determining the enantiomeric excess of optically active phosphiranes as part of their report into the synthesis of such compounds.[184] Marinetti reported that addition of enantiomerically pure (*R*)-styrene oxide to molybdenum complex **143** yielded diastereomeric (phosphirane)$Mo(CO)_5$ complexes with the phosphirane then liberated by a ligand displacement reaction with 1,2-*bis*(diphenylphosphino)ethane. It was then reported that addition of the resultant phosphirane to $(COD)_2RhPF_6$ produced a diastereomeric series of rhodium compounds of which the *meso* and chiral complexes are easily differentiated by ^1H NMR spectroscopy (Scheme 84).



Scheme 84 - Formation of diastereomeric rhodium complexes to determine the enantiomeric excess of phosphiranes by ^{1}H NMR spectroscopy

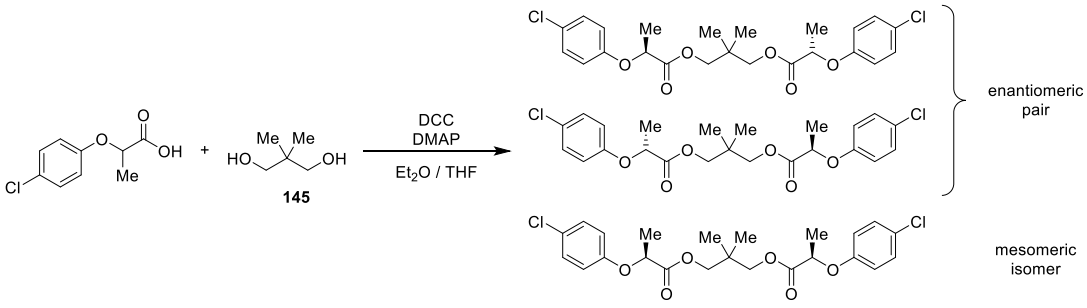
Grotjahn *et al.* reported a method for measuring the enantiopurity of chiral amines which employed non-chiral derivatization agent **144**.[185] By dimerization of (*rac*)-α-methylbenzylamine using triphosgene and triethylamine, a Horeau series of diastereomeric ureas were synthesised (Scheme 85).



Scheme 85 - Formation of diastereomeric urea complexes for determining the enantiopurity of chiral amines

Analysis of the ^{1}H NMR spectrum of this diastereomeric mixture showed two doublets around δ1.30 ppm corresponding to the *meso* and enantiomeric pair of diastereomers in a ratio of 1:1.04 ±0.05, showing good agreement with the expected 1:1 ratio for a racemic compound.

The use of a diol template to form diastereomeric dimers of chiral carboxylic acids was reported by Heumann *et al.* to determine their enantiomeric excess.[186] After investigating a number of diol templates, 2,2-dimethyl-1,3-propanediol **145** was found to be the most effective reagent with esterification proceeding with no kinetic resolution, or epimerisation of the acid (Scheme 86).



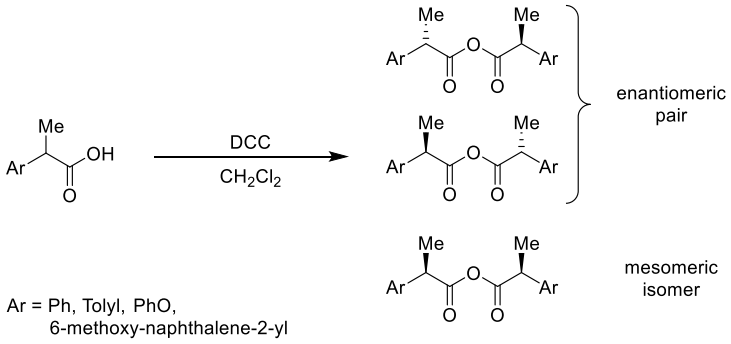
Scheme 86 - Esterification with an achiral diol for determining the enantiomeric excess of carboxylic acids

Heumann demonstrated that ^{1}H NMR spectroscopic analysis of the resultant diesters gave clearly defined resonances for the *meso* and enantiomeric complexes with the enantiomeric excess of the carboxylic acids inferred from integration of these resonances. This protocol was employed to determine enantiomeric excess up to 99% with a high degree of accuracy.

Platzer *et al.* reported another method for determining the enantiomeric excess of carboxylic acids by formation of praseodymium dimers.[187] By reaction of carboxylates with tris(tetraphenylimidodiphosphinato)praseodymium a series of diastereomeric praseodymium dimer species were formed. The enantiomeric excess of the carboxylic acid was able to be determined from a number of baseline separated resonances in the ^{1}H NMR spectrum of the diastereomeric mixture.

More recently, Eames *et al.* reported another protocol for determining the enantiomeric excess of chiral carboxylic acids.[188] However, unlike the method

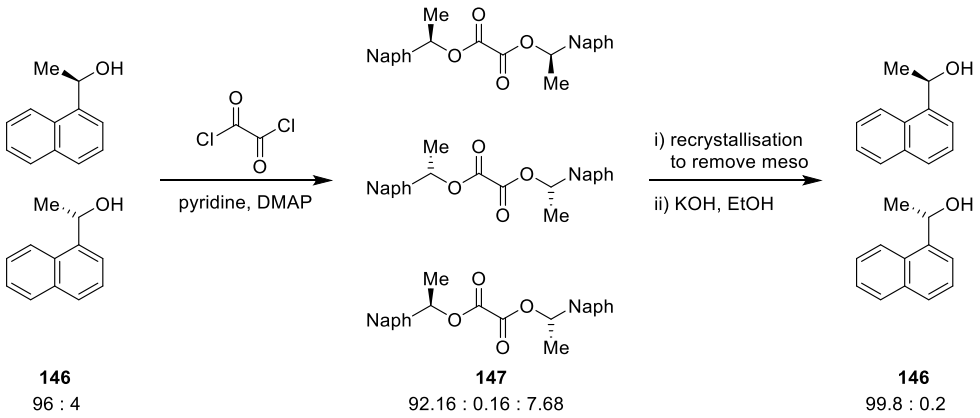
reported by Heumann,[186] Eames' method removed the need for a coupling template and instead, with a direct coupling between two carboxylic acid molecules being used to form diastereomeric complexes (Scheme 87).



Scheme 87 - Direct homocoupling of α-aryl carboxylic acids in order to determine their enantiomeric excess

4.1.3 Enantioenrichment of Intermediates during Synthesis

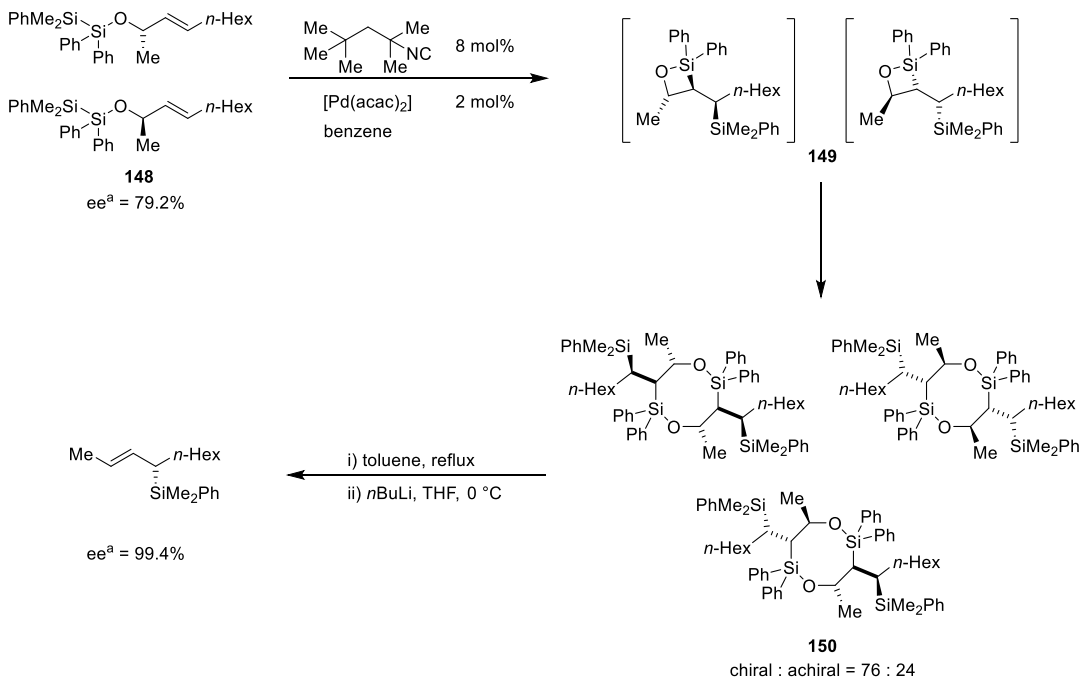
There have been a number of reports in the literature where the phenomenon discovered by Horeau[173] has been used to enantioenrich intermediates during synthetic protocols. Fleming *et al.* reported one such exploitation during the synthesis of nonactin.[189,190] Using Horeau's method Fleming was able to demonstrate the enantioenrichment of of (1*R*)-1-(1'-naphthyl)ethanol **146** from 92% to essentially enantiopure levels by dimerization to form an oxalate *bis*-ester **147** (Scheme 88).



Scheme 88 - Enantioenrichment of naphthalene alcohol 146 during the synthesis of nonactin

After derivatization, removal of the *meso* compound from the diastereomeric mixture was achieved through recrystallization, leading to an enantiomeric mixture with an enhanced enantiomeric excess of 99.6%. The oxalates were then hydrolysed to return the naphthalene alcohol **146** which has its enantiopurity enhanced from 92% to 99.6%, albeit with a loss of yield due to removal of the *meso* diastereomer.

As part of their reported synthesis of (*E*)-allylsilanes, Suginome and co-workers used the formation of cyclic dimer intermediates from disilanyl ethers of moderate enantiomeric excess (79.2% *e.e.*), in order to synthesise the desired allylsilanes with enhanced enantiopurities (Scheme 89).[191]

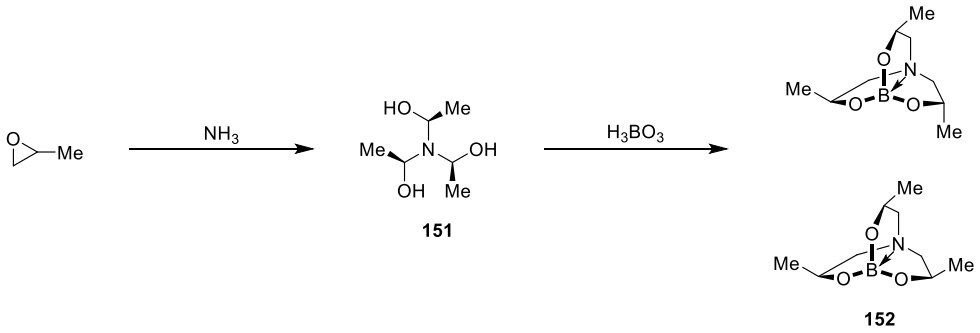


Scheme 89 - Enantioenriched synthesis of (*E*)-allylsilanes

In order to achieve the enhancement, Suginome's synthetic protocol starts with disilanyl ether **148** of 79.2% enantiomeric excess which undergoes intramolecular *bis*-silylation, catalysed by palladium(II) acetylacetonate, to give oxasiletane **149**. This subsequently dimerises to form cyclic species **150**. The dimerization step forms three diastereomeric species, two of which are an enantiomeric pair and the other of which is the *meso* compound. The chiral material in this mixture was removed by recrystallization and although this led to a loss of around 24% of the overall yield, this chiral material had an enhanced enantiomeric excess of 99.4%. This enhancement occurs as a result of a large portion of the minor enantiomer of the disilanyl ether starting material being removed *via* incorporation into the *meso* compound.

Farina *et al.* demonstrated an extension to the Horeau method which utilised the formation of trimers to enhance the enantiopurity of triisopropanolamine for the synthesis of different stereoisomers of trimethylboratrane **152**.[192] Three equivalents of scalemic propylene oxide were added to ammonia solution to form triisopropanolamine (Scheme 90) and it was discovered that small amounts of the

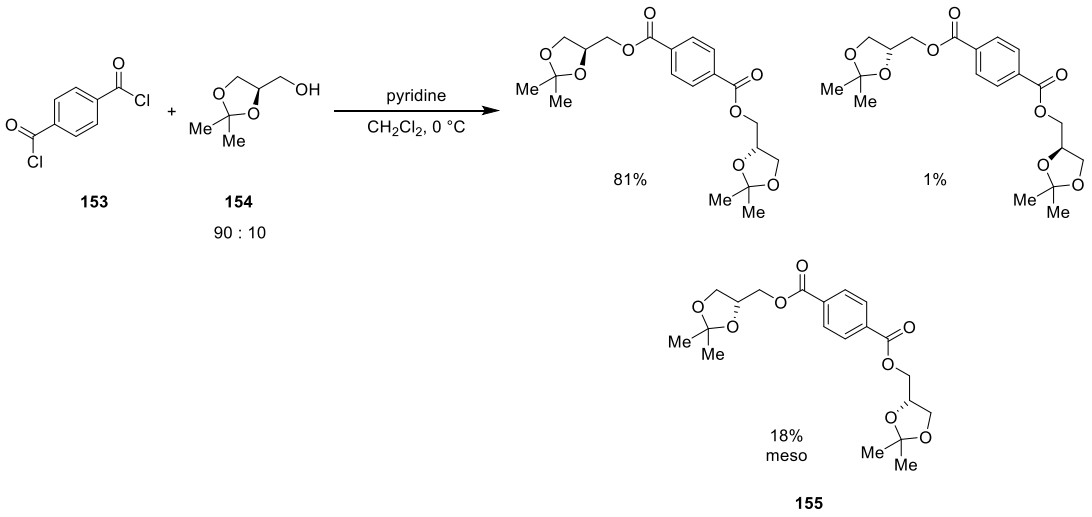
undesired propylene oxide isomer had no effect on the enantiopurity of the symmetrical triisopropanolamine isomer **151**.



Scheme 90 - Enantioenhancement of triisopropanolamine by trimerisation

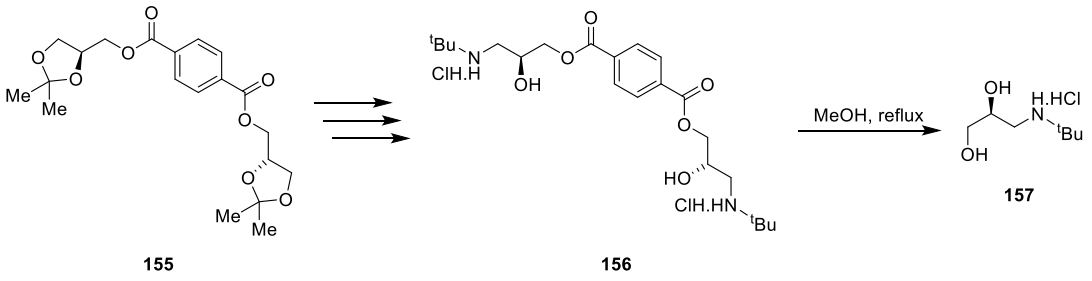
Farina concluded that trimerisation could potentially become a more powerful tool for enhancement of the enantiopurity of intermediates and that the technique could be further extended to the formation of tetramers. However, tetramerisation would potentially result in a large number of side products which would need to be removed, reducing the overall yield of the target molecule and so in practice is likely to be a less useful technique.

Servi *et al.* used Horeau's approach to enantioenrich key intermediate **155** in the synthesis of an amino alcohol intermediate **157** used for the industrial synthesis of (*S*)-timolol.[193] Using terephthaloyl dichloride **153** as a linker to join two molecules of isopropylideneglycerol **154**, Servi was able to synthesise the resultant diester in an enhanced enantiopurity (Scheme 91).



Scheme 91 - Enantioenrichment of diester 155 using an achiral *bis*-acid chloride 153

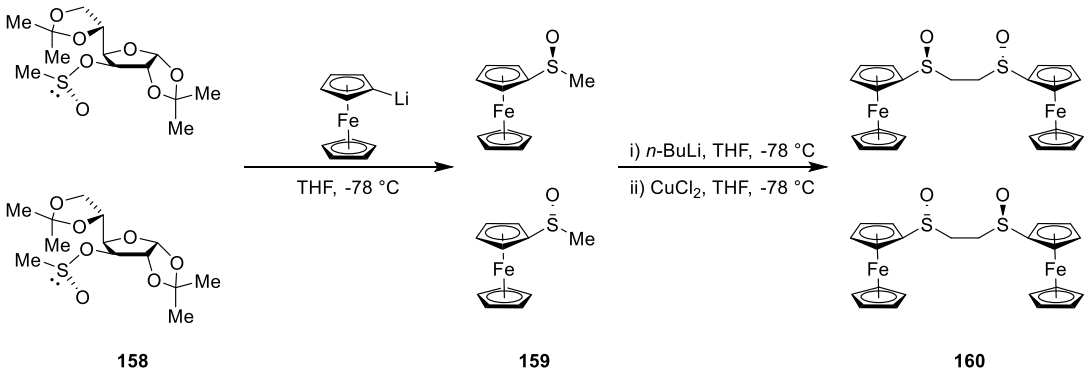
The *meso* compound was easily removed in a single recrystallization when seeded with the desired enantiomer. The enantiopurified diester was then taken through to the *tert*-butylamino derivative **156** which was then converted to the amino alcohol **157** by refluxing in methanol (Scheme 92).



Scheme 92 - The use of enantioenriched diester 155 for the synthesis of timolol intermediate 157

This enantioenriching synthesis yielded enantiopure (*S*)-1-(*tert*-butylamino)propane-2,3-diol hydrochloride **157**, a key intermediate in the industrial synthesis of (*S*)-timolol, eliminating the need to use strictly enantiopure isopropylideneglycerol **154** as a reagent.

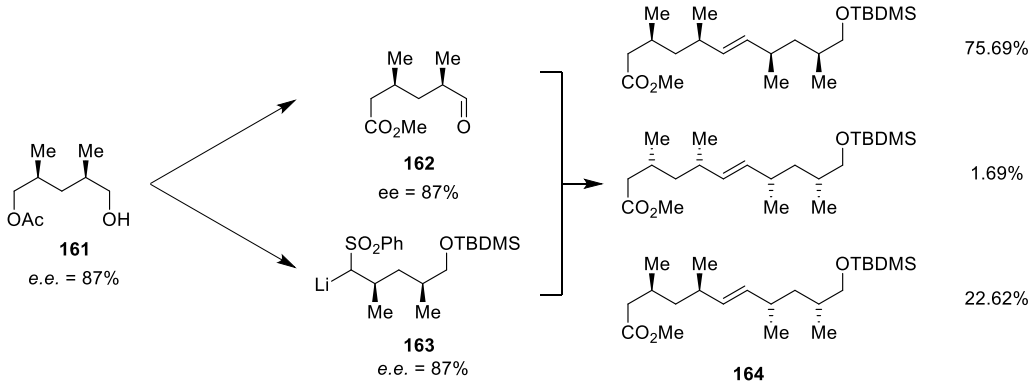
Recently, Khiar *et al.* have shown how the Horeau method can be used to synthesise enantiopure *bis*-sulfoxide ligands for use in the 1,4-addition of boronic acids to electron deficient alkenes.[194] Diacetone-D-glucose methanesulfinate **158** was treated with ferrocenyllithium to form the methylsulfoxide **159** which subsequently underwent copper catalysed oxidative dimerization to afford the desired *bis*-sulfoxide ligand **160** (Scheme 93).



Scheme 93 - Enantiomerically enhanced synthesis of a ferrocenyl *bis*-sulfoxide ligand

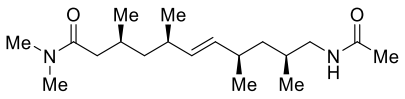
Due to the dimerization step, Khiar was able to synthesise the *bis*-sulfoxide ligands with an enhanced enantiopurity based on the parent methylsulfoxide by removal of the (*R*,*S*)-*meso* compound by column chromatography. This synthetic protocol produced C_2-symmetric ligands in high enantiomeric purity which were then used for the enantioselective 1,4-addition of boronic acids to alkenes with enantiomeric excesses of the resultant cyclic ketones as high as 97%.

In 2002, Hoffmann *et al.* reported a Horeau amplification for an important intermediate as part of their synthetic protocol for the preparation of a conformationally flexible β-hairpin mimetic.[195] These types of structures are designed to be incorporated into peptidic structures in order to create foldamers. Alcohol **161** was used to synthesise the two building blocks **162** and **163** which were subsequently coupled using a Julia-olefination (acetylation and Na/Hg reduction) to yield the (*E*)-alkenoate **164** (Scheme 94).



Scheme 94 - Enantiomerically amplified synthesis of (*E*)-alkenoate intermediate 164

Although the enantiomeric excesses of the starting alcohol **161** and the two building blocks **162** and **163** were 87%, due to a Horeau amplification, the Julia-olefination coupling reaction resulted in the desired enantiomer of the alkenoate product being produced in an enhanced enantiomeric excess. The undesirable *meso*-diastereomer could be removed by flash column chromatography leaving the desired compound in 98% enantiomeric excess. This highly enantiopure material was then converted *via* four further transformations into β-hairpin mimetic **165** (Figure 39).

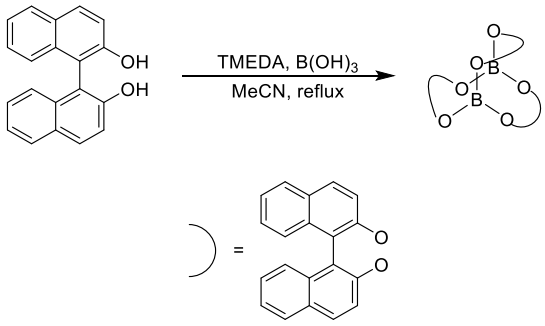


165

Figure 39 - β-hairpin mimetic 165

4.1.4 Enantioenrichment of Chiral Substrates

The Horeau principle has also been applied by a number of groups for the enantioenrichment of chiral substrates by kinetic resolution, whereby a substrate of moderate to high enantiomeric excess can by enhanced to essentially enantiopure levels.[196] BINOL is an important chiral ligand for asymmetric organic synthesis and thus a method for obtaining a single enantiomer of BINOL in a quick and simple manner is highly desirable. Periasamy *et al.* demonstrated such a method by forming B_2L_3 complexes from scalemic BINOL and boric acid, where each BINOL unit bridges between the two boron atoms (Scheme 95).[197] NMR data suggested the formation of a propeller complex previously reported by Kaufmann.[198]

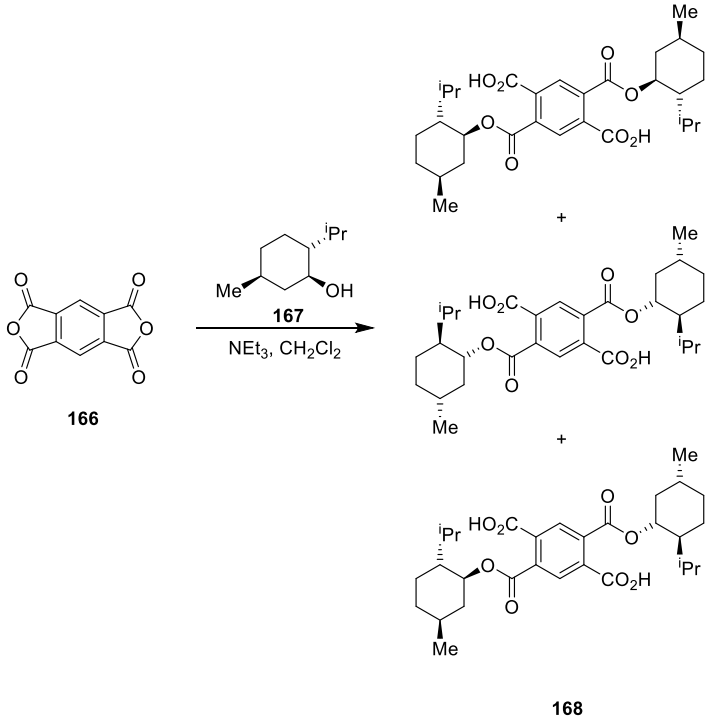


Scheme 95 - Formation of a B_2L_3 complex to enhance the enantiopurity of BINOL

The optimal conditions for this method were reported to be with a 5:2 ratio of BINOL to boric acid, refluxed in acetonitrile. TMEDA was then added to the

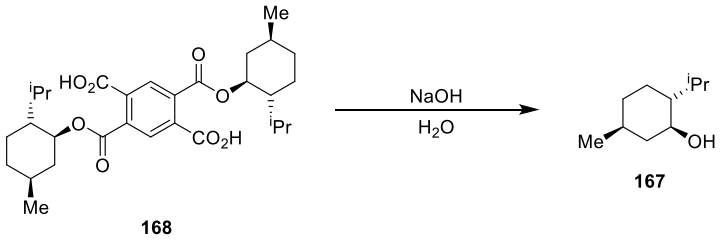
reaction mixture which caused the symmetrical *RRR* or *SSS* complex to be precipitated in high enantiomeric excess leaving a soluble mixture of low *e.e.* complexes behind in the filtrate. The enantioenriched BINOL was then liberated from the symmetrical complex by addition of dilute HCl. This enrichment protocol proved highly successful with scalemic BINOL of 52% *e.e.* being enriched to 95%.

In 2008, Paine *et al.* demonstrated the application of the Horeau principle to enrich the enantiomeric excess of commercial samples of scalemic menthol.[199] As part of their research into using *para* diesters of menthol as resolving agents for chiral amines it was shown that commercially available scalemic D-menthol **167** could be used to form diesters with pyromellitic dianhydride **166**. A series of diastereomers **168** were formed, with the homochiral *para* enantiomeric pair being removed from the reaction mixture by fractional recrystallization (Scheme 96).



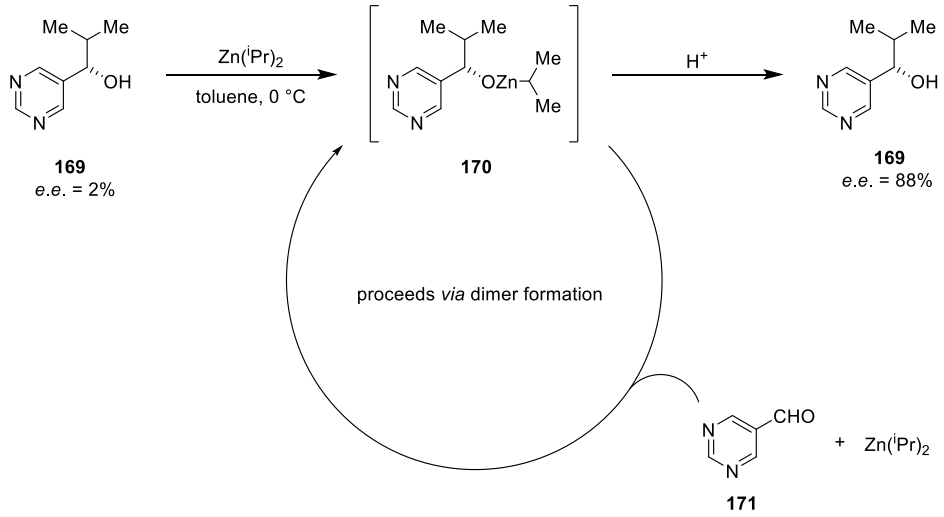
Scheme 96 - Chiral purification of D-menthol 167 *via* formation of diesters

The *para*-diester obtained from the crystallization was of an increased enantiopurity compared to the scalemic menthol due to removal of the L-enantiomer through its incorporation in the *meso* compound. The desired D-menthol is then liberated from the diester by base hydrolysis with sodium hydroxide to yield the desired enantiomer with a chiral enhancement from 96% to 99.95% *e.e.* (Scheme 97).



Scheme 97 - Liberation of essentially enantiopure D-menthol after diester formation

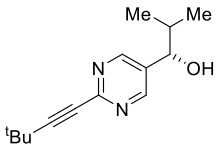
Research into the origins of homochirality in nature[200] has also led to the discovery of systems that are able to enhance the enantiopurity of chiral substrates through autocatalysis.[201,202] In 1995, Soai *et al*. reported the amplification of the enantiomeric excess of a 5-pyrimidyl alkanol **169** from 2% to 88% by reaction with diisopropylzinc and pyrimidine-5-carboxaldehyde **171** (Scheme 98).[203]



Scheme 98 - Enantioenrichment of 2-methyl-1-(5-pyrimidyl)propan-1-ol 169 by autocatalysis

In this autocatalytic process Soai reported that pyrimidyl alcohol **169** of low enantiomeric excess reacts with diisopropylzinc to form alkoxide intermediate **170**. This compound then acts as an improved catalyst for the addition of diisopropylzinc to pyrimidine-5-carboxaldehyde **171** yielding further amounts of alkoxide **170** with an increased enantiomeric excess. This alkoxide is then hydrolysed to pyrimidyl alcohol **169** of an improved enantiomeric excess which can be cycled back into the protocol to sequentially increase the enantiomeric excess up to 88%.

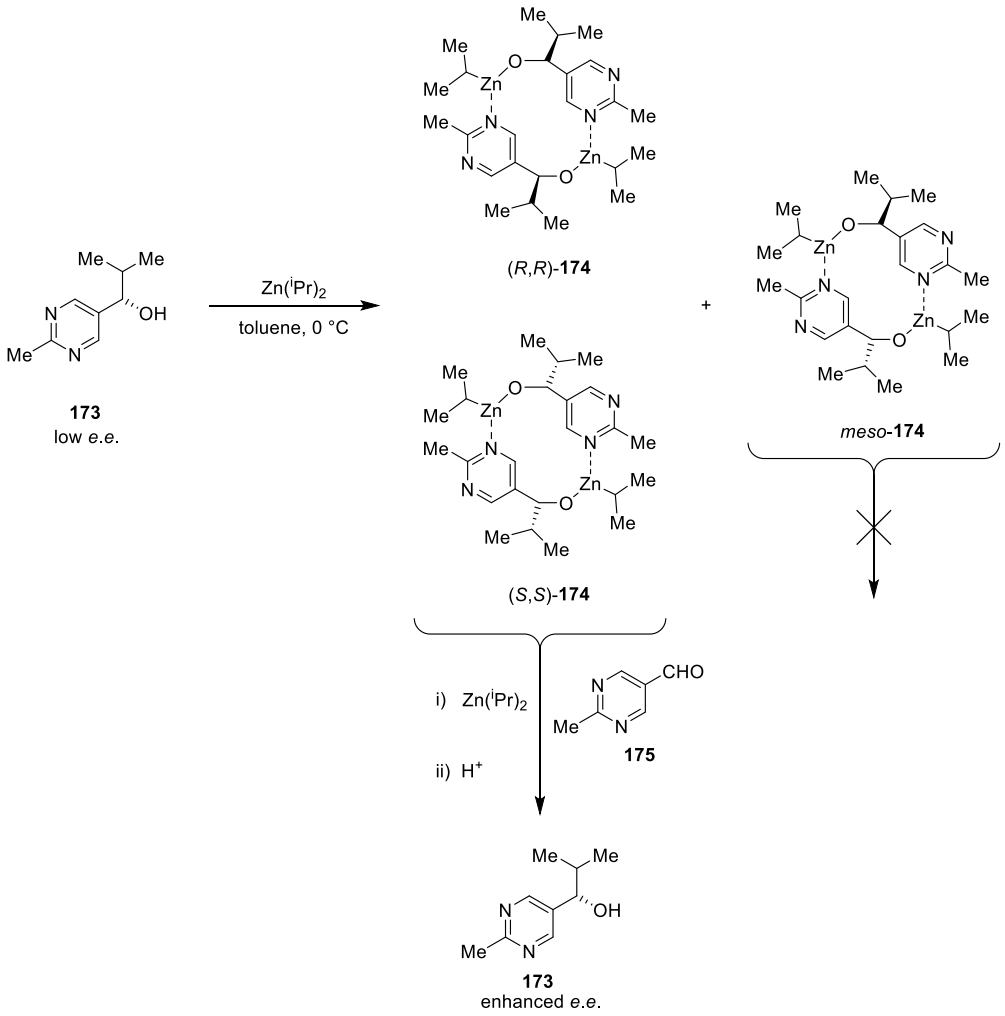
Soai *et al*. then published an improved model for autocatalysis in 1999 and reported that functionalization of the pyrimidyl ring at the 2-position with an alkynyl group increased the enantioselectivity of the autocatalyst, yielding pyrimidyl alkanols with >99.5% enantiomeric excess and in a 99% yield. To achieve these high levels of conversion and enantioselectivity, 1-(2-*tert*-butylethynyl-5-pyrimidyl)-2-methyl-1-propanol **172** was employed as autocatalyst (Figure 40).



172

Figure 40 - The structure of autocatalyst 1-(2-tert-butylethynyl-5-pyrimidyl)-2-methyl-1-propanol 172

The mechanism of Soai's autocatalysis reaction has been investigated by Blackmond *et al*. and was reported to involve formation of a series of diastereomeric dimers which provide a positive non-linear effect akin to Kagan's ML_n model (Scheme 99).[204]



Scheme 99 - Formation of diastereomeric dimer catalysts in Soai's autocatalysis reaction

Blackmond reported that the *meso* diastereomer **174** is inactive as a catalyst leading to an enantioenhancement and positive non-linear effect in the same manner as reported by Horeau and Kagan.[205] The homochiral diastereomeric dimers formed from two molecules of pyrimidyl alcohol **173** and diisopropylzinc position the Zn atoms well for coordination to aldehyde **175**, this is then attacked by diisopropylzinc yielding the enantioenhanced alkoxide which after hydrolysis gives the desired pyrimidyl alcohol **173** in a higher enantiomeric excess.

More recently, Blackmond *et al*. have proposed alternative intermediate species, dimer **176** and tetramer **177**, derived from ^{1}H NMR analysis and DFT calculations

that could be acting as the active catalyst species in the autocatalytic cycle (Figure 41).[206]

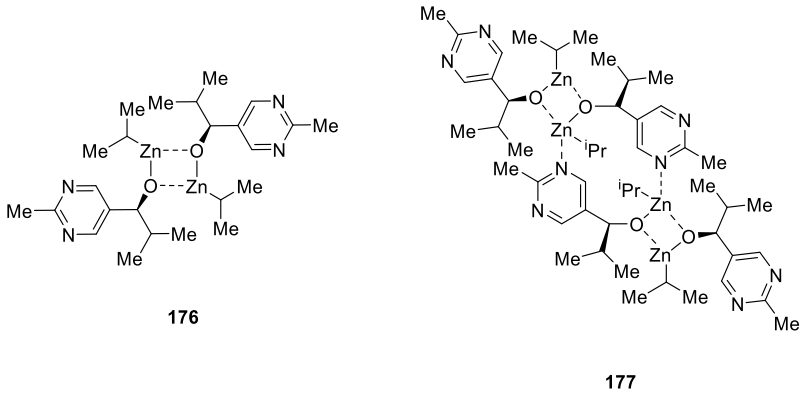


Figure 41 - The structures of dimer 176 and tetramer 177: autocatalysis intermediates proposed from ^{1}H NMR analysis and DFT calculations

In 2007, Blackmond reported the formation of hydrogen bonded diastereomeric complexes in solution as a method of enantioenrichment of amino acids.[207] It was reported that treatment of scalemic solutions of amino acids with carboxylic acid additives such as fumaric acid and oxalic acid led to an increase in the enantiomeric excess of the amino acid in solution. This effect is due to the formation of diastereomeric hydrogen bonded complexes, with the solubility of the heterochiral complex being greatly inhibited (Figure 42), leading to its crystallization out of solution, leaving behind a solution of enhanced enantiopurity.

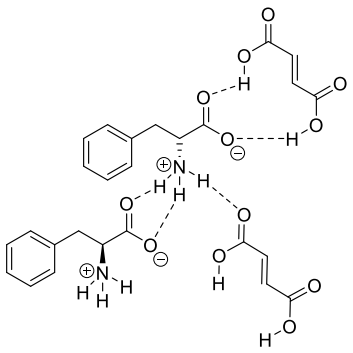
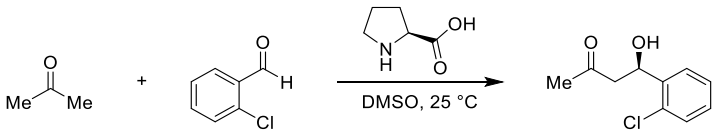


Figure 42 – Proposed structure of the heterochiral diastereomeric complex formed between phenylalanine and fumaric acid

Enantioenhancement in solution was reported for a range of chiral amino acids, with enhancement to essentially enantiopure levels reported for leucine with oxalic acid as an additive, and the use of fumaric acid as an additive for both valine and phenylalanine.

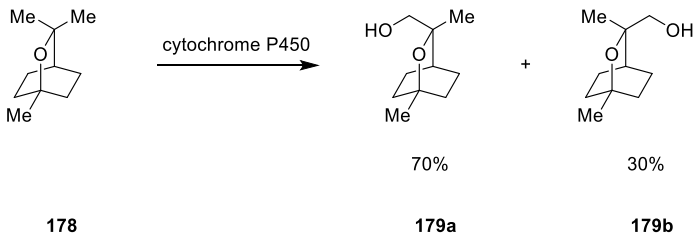
The phenomenon of amino acids having a different enantiomeric excess in solution compared to the solid state has been reported to occur without carboxylic acid additives as well. In 2006, Blackmond reported that scalemic proline exhibits an enantiomeric excess of 50% as a solution in DMSO whilst scalemic serine, at its eutectic point in water, exhibits an enantiomeric excess of >99% in solution under solid-liquid equilibrium conditions.[208] At high catalyst concentrations where solid amino acid is in equilibrium with dissolved amino acid, the solid is composed of 1:1, L:D crystals, with the solution exhibiting a higher enantiomeric excess by removal of material of low enantiomeric excess in the crystalline phase. These solutions were then shown to cause enantioenhancement in proline catalysed aldol reactions, since, despite solid proline of low enantiomeric excess being present, the available catalyst in the solution phase is of higher enantiomeric excess (Scheme 100).



Scheme 100 - L-proline catalysed aldol reaction

Blackmond noted that non-linear effects in asymmetric catalysis may not be, in every case, explained by Kagan's ML_n model but may be caused by this type of physical phase behaviour.[209]

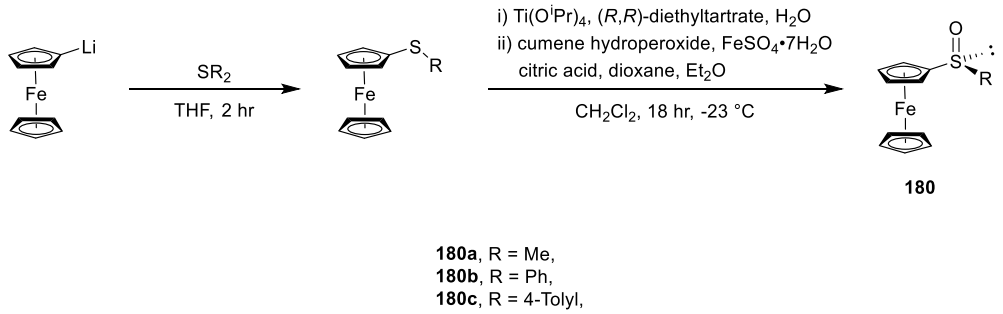
In 1991, Carman *et al*. reported the fractionation of scalemic natural product **179** on preparative HPLC silica gel columns.[210] Cineole **178** is converted to alcohol **179** by the female Australian brushtail possum and excreted through urine (Scheme 101).



Scheme 101 - The female brushtail possum converts cineole 178 into alcohols 179a and 179b in a 40% enantiomeric excess

It was reported that chromatography of a sample of **179** of 40% enantiomeric excess caused fractionation on the achiral silica gel column affording initial fractions containing **179** in an 80% enantiomeric excess. It was hypothesised that this was due to the adhesion of a chiral moving phase onto the silica gel column thereby essentially converting it into a chiral HPLC column. The enantiomeric excess of fractions obtained from the column was shown to decrease over time thereby providing initial fractions in an enhanced enantiomeric excess.

This phenomenon was also reported by Kagan *et al*. in 1994 using preparative flash column chromatography.[211] It was reported that purification of chiral sulfoxides of scalemic optical purity with a silica gel flash chromatography column led to fractionation of the enantiomers on the column to give the first eluted fractions of the chiral sulfoxide in enhanced enantiomeric excess, whilst later eluted fractions had a depleted enantiomeric excess. Kagan synthesised a range of chiral sulfoxides **180a-c**[212] including a number of ferrocenyl derivatives (Scheme 102) and used this fractionation method to enhance their enantiomeric excess.



Scheme 102 - General synthesis of ferrocenyl chiral sulfoxides 180a-c

Kagan reported that this chromatography method was able to enhance the enantiopurity of ferrocenyl methyl sulfoxide **180a** from 90.5% to 99.5% in the first fractions off the silica gel flash chromatography column. For ferrocenyl phenyl sulfoxide **180b** the enantioenhancement occurred in the final fractions, with material of 65% enantiomeric excess being amplified to 94%. This was proposed to be due to the formation of diastereomeric sulfoxide species which have different chromatographic mobilities leading to different retention times on the column for homochiral and heterochiral diastereomers.

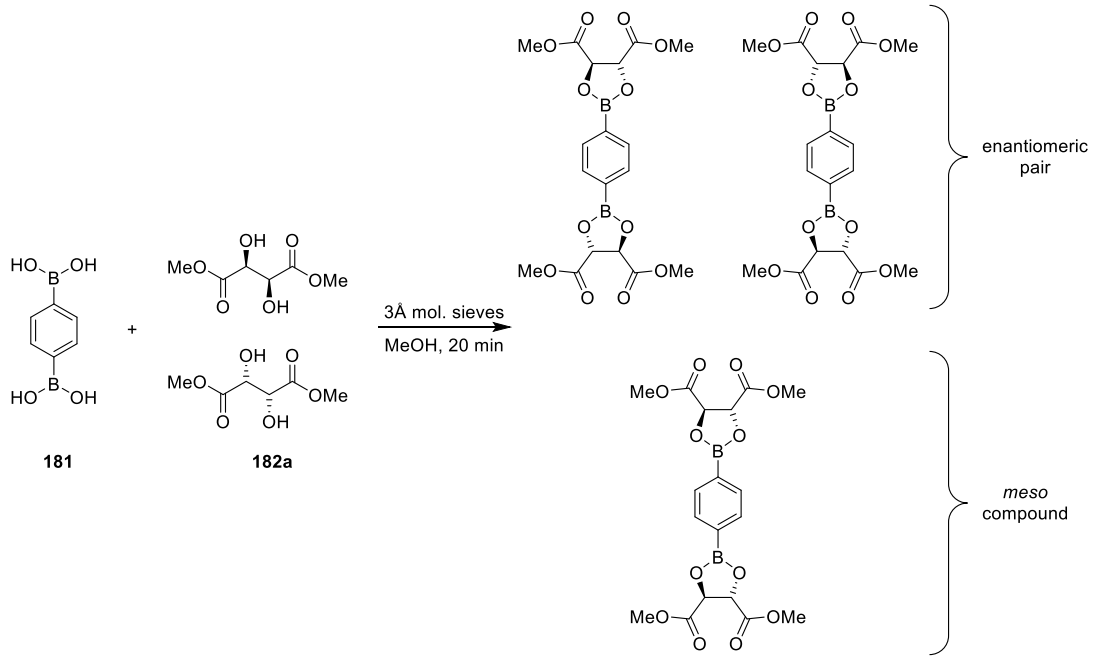
In summary, the Horeau principle has been employed by a number of groups as a tool to determine the enantiomeric excess of chiral substrates by formation of a series of diastereomers which are identifiable by NMR spectroscopy. The technique

has also been demonstrated for enhancing the enantiomeric excess of chiral molecules, either as part of a synthetic protocol, or *via* kinetic resolution of substrates such as BINOL and menthol. Formation of a Horeau series of homochiral and heterochiral diastereomers has also been demonstrated to be behind the theory for non-linear effects in asymmetric catalysis such as Kagan's ML_n model.

4.2 Results and Discussion

The Horeau principle enables the use of a non-chiral template to be used to form diastereomeric complexes which can then be used to determine the enantiomeric excess of a chiral substrate by NMR spectroscopy. Traditional chiral derivatization protocols, employ the use of a chiral molecule, as well as, on occasion, other building blocks to form chiral recognition complexes. This chiral derivatization agent needs to be enantiopure in order to determine the enantiomeric excess of a substrate accurately or the diastereomeric excess of the complexes formed will not reflect that of the starting enantiomeric material. These enantiopure chiral derivatization agents are often very costly and can require a number of reaction steps and purifications if they are to be recycled after derivatization. Therefore, it was decided to develop a protocol that would employ a cheap, non-chiral bifunctional template to determine the enantiopurity of chiral diols.

Our first attempt to develop a new protocol for determining the enantiomeric excess of chiral diols involved reacting dimethyl-DL-tartrate **182a** with 1,4-phenyldiboronic acid **181**, in the presence of 3Å molecular sieves added to remove water from the system and drive the equilibrium towards ester formation. It was postulated that the two enantiomers of the diol would react in a statistical manner to yield a Horeau series of diastereomeric boronate ester complexes, forming an enantiomeric pair and a *meso* compound (containing a plane of symmetry through the central benzene ring) which could potentially be distinguished by ^{1}H NMR spectroscopy (Scheme 103).

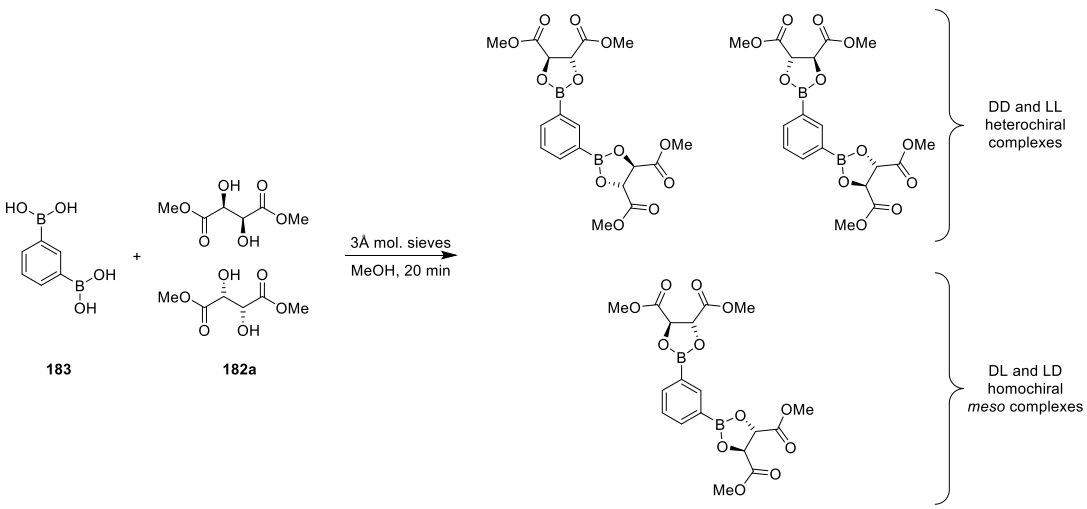


Scheme 103 - Formation of a Horeau series of boronate esters from dimethyl-DL-tartrate 182a and 1,4-phenyldiboronic acid 181

Methanol was found to be the best solvent for full conversion of the starting materials into the resultant esters, since the parent 1,4-diboronic acid template **181** was only sparingly soluble in chlorinated solvents, and only partial conversion was achieved in solvents such as tetrahydrofuran and acetone. Boronate ester formation was confirmed by ^{1}H NMR spectroscopy in deuterated chloroform, since the free boronic acid is not soluble in $CDCl_3$, whilst ^{11}B NMR spectroscopy revealed a single boronate ester resonance at 31.7 ppm. Although clean formation of the boronate esters was confirmed, there were no diastereomeric protons observed in the 500MHz ^{1}H NMR spectrum of the resultant mixture indicating that 1,4-phenyldiboronic acid **181** was not a suitable achiral bifunctional template for enantiomeric excess determination.

With this knowledge in hand it was postulated that the distance between the two chiral units in the diastereomeric complex formed between 1,4-phenyldiboronic acid **181** and dimethyl-DL-tartrate **182a** was too large to achieve any kind of chiral recognition. Thus 1,3-phenyldiboronic **183** was next employed as a template and

reacted with dimethyl-DL-tartrate **182a** in methanol in the presence of 3Å molecular sieves, since this commercially available template would bring the two chiral units of its derived *bis*-boronate ester closer in space (Scheme 104).



Scheme 104 - Formation of a Horeau series of boronate esters from dimethyl-DL-tartrate 182a and 1,3-phenyldiboronic acid 183

As with the 1,4-boronate complexes, the formation of these 1,3-boronate complexes was confirmed by ^{1}H NMR spectroscopy in deuterated chloroform, since free 1,3-phenyldiboronic acid **183** is not soluble in $CDCl_3$. A single boronate resonance was also seen at 31.7 ppm in the ^{11}B NMR spectrum of the resultant diastereomeric mixture and the $[M + Na]^+$ seen in the mass spectrum.

Analysis of the 500 MHz ^{1}H NMR spectrum in a number of deuterated solvents including deuterated benzene, methanol, tetrahydrofuran and water showed no diastereomeric protons present, however, when the ^{1}H NMR spectrum was obtained in deuterated chloroform a pair of diastereomeric protons were seen for the phenyl proton at the 2-position of the central aryl core at 8.48 ppm (Figure 43).

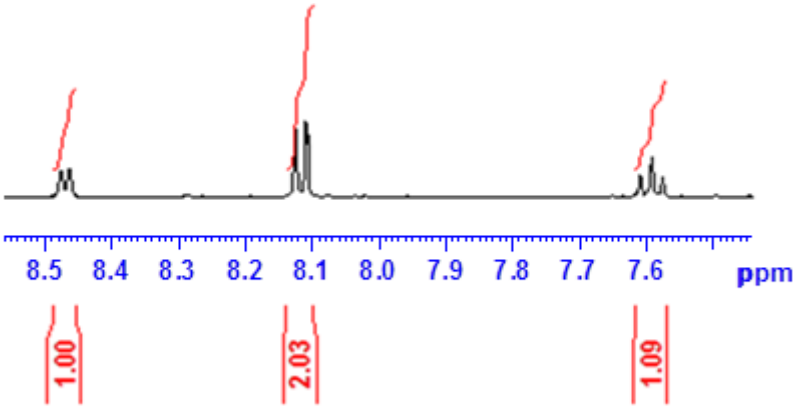


Figure 43 – Expansion of the aryl region of the 500 MHz ^{1}H NMR of the diastereomeric mixture formed from racemic dimethyl-DL-tartrate 182a and 1,3-phenyldiboronic acid 183 showing splitting of the 2-phenyl proton at 8.48 ppm

Integration of these diastereomeric resonances showed a 50:50 ratio of homochiral and heterochiral diastereomers formed in the reaction which is in perfect agreement with the ratio expected for a sample of racemic dimethyl-DL-tartrate **182a**. The spectrum was then compared with the 500 MHz ^{1}H NMR of the complex formed from enantiopure dimethyl-L-tartrate and 1,3-phenyldiboronic acid **183** which revealed, as expected, no diastereomeric splitting and only a single resonance for the 2-phenyl proton at 8.48 ppm (Figure 44).

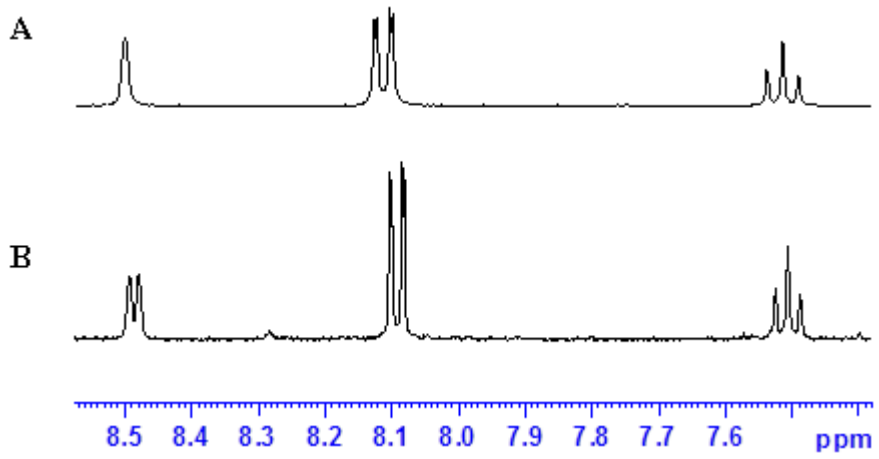


Figure 44 - Comparison of the 500 MHz ^{1}H NMR spectrum of the boronate ester complex formed from enantiopure dimethyl-L-tartrate and 1,3-phenyldiboronic acid 183 (A) and of the 500 MHz ^{1}H NMR spectrum of the diastereomeric mixture formed from racemic dimethyl-DL-tartrate 182a and 1,3-phenyldiboronic acid 183

A pair of diastereomeric resonances were also seen for the methoxy protons of the dimethyl-DL-tartrate fragment of the resultant boronate esters at 3.91 ppm, thus providing diagnostic protons for both the chiral and achiral fragments of the boronate ester derivatives (Figure 45).

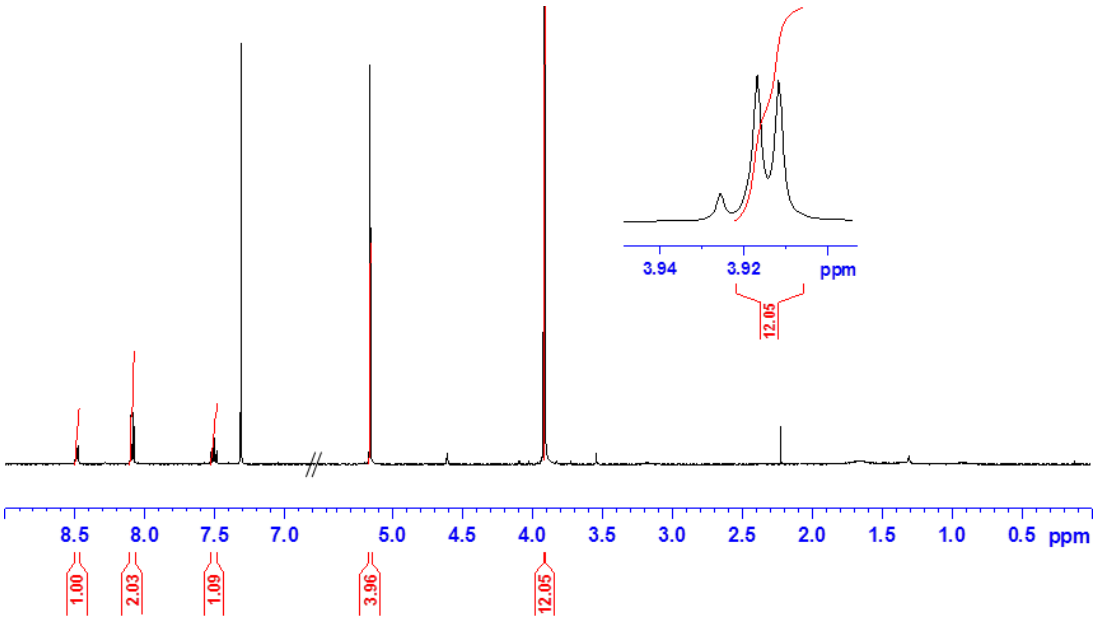


Figure 45 – 500MHz ^{1}H NMR of the diastereomeric mixture formed from racemic dimethyl-DL-tartrate 182a and 1,3-phenyldiboronic acid 183 with expansion of the diastereomeric methoxy region at 3.91 ppm

In contrast to conventional chiral derivatization protocols in which the diastereomeric excess measured from integration of the ^{1}H NMR spectrum directly affords the enantiomeric excess of the employed chiral substrate, integration of the ^{1}H NMR spectrum obtained from a Horeau-type derivatization protocol does not directly give the enantiomeric excess of the chiral substrate. The diastereomeric resonances arise from homochiral (*RR* and *SS*) and heterochiral (*RS* and *SR*) diastereomers and thus the diastereomeric excess needs to be converted to the true enantiomeric excess by consideration of the statistical model discussed previously. This measured diastereomeric excess, taken from measurement of the relative homochiral and heterochiral resonances, is related to the true enantiomeric excess of the chiral substrate by the quadratic relationship reported by Horeau.[173] Horeau reported that the enantiomeric purity (p) is calculated from the integrated peak areas for the homochiral (Q) and heterochiral (Q') resonances and that $p^2 = (K-1)/(K+1)$. If the enantiopurity of the material with *R* stereochemistry is assumed to be *x* and the enantiopurity of the material with *S* stereochemistry is assumed to be (1-*x*) then relationships for the *RR* (x^2), *SS* $(1-x)^2$ and *meso* ($2x(1-x)$) can be derived. These relationships can be used to generate the curve shown in Figure 46 which shows

how the measured diastereomeric excess (homochiral – heterochiral) relates to the enantiomeric excess of the starting diol (*R*-*S*).

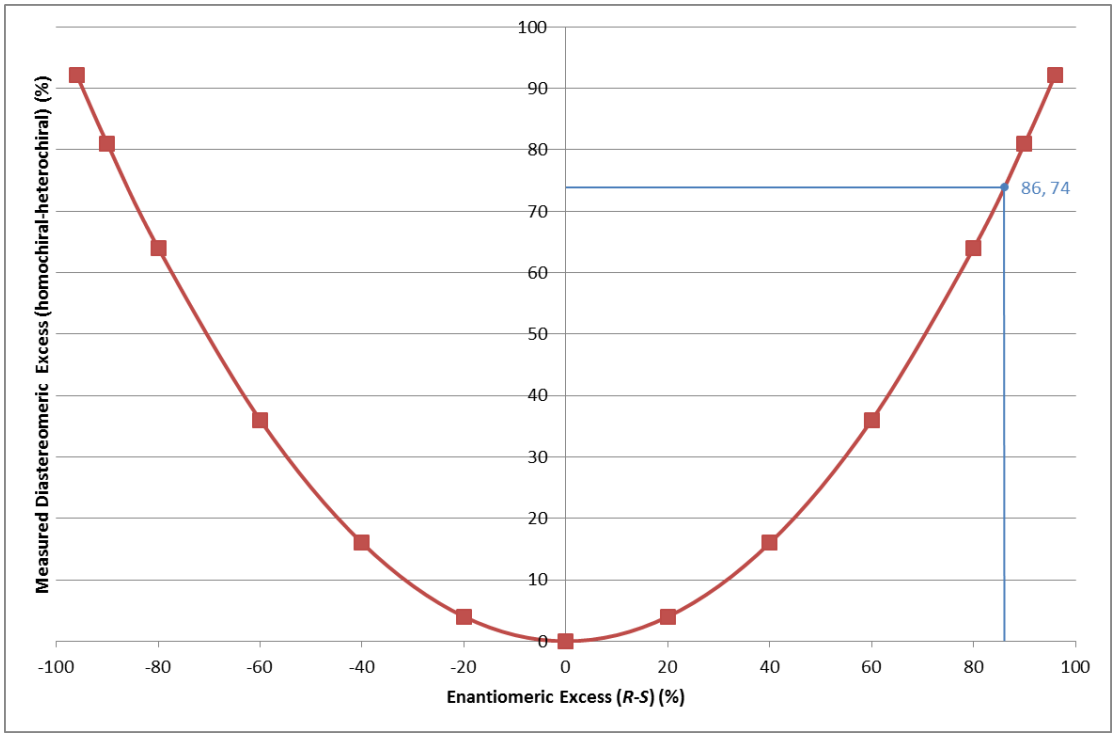


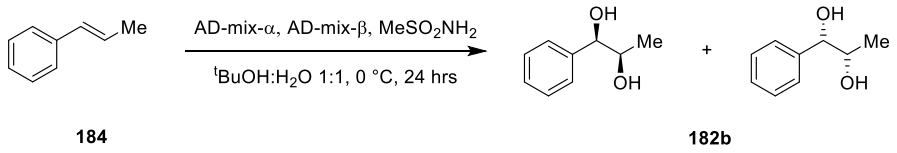
Figure 46 - Relationship between the measured diastereomeric excess (homochiral-heterochiral) and the enantiomeric excess of a chiral substrate after Horeau-type derivatization

The above graph is applicable to any dimeric Horeau-type derivatization and can be used to easily infer the enantiomeric excess of the chiral substrate employed in derivatization, for example, a measured diastereomeric excess of 74% corresponds to a substrate enantiomeric excess of 86%. Due to the quadratic relationship between the enantiomeric excess and measured diastereomeric excess both a positive and negative value of enantiomeric excess are possible for each value of diastereomeric excess. Thus, although this technique is able to determine enantiomeric excess, it is unable to determine which enantiomer is present in excess within a scalemic sample.

4.2.1 Synthesis of Chiral Diols Using Sharpless Dihydroxylation Reaction

In order to determine the scope and limitations of this new chiral derivatization protocol a number of chiral diols which were not commercially available were synthesised since, our new *bis*-boronic acid template protocol was most likely to be useful for determining the enantiomeric excess of chiral diols produced in asymmetric protocols.

Trans-β-methylstyrene was reacted with a mixture of AD-mix-α, AD-mix-β and methanesulfonamide in 1:1 *tert*-butanol and water at 0 °C for 24 hours in a Sharpless dihydroxylation reaction to afford the corresponding racemic mixture of (*R*,*R*)-diol **182b** and (*S*,*S*)-diol **182b** (Scheme 105).[213]

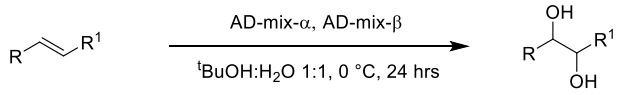


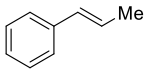
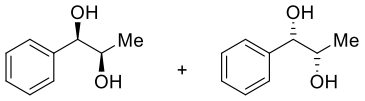
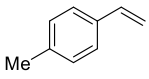
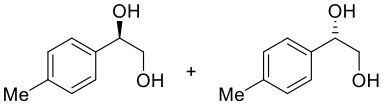
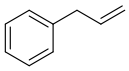
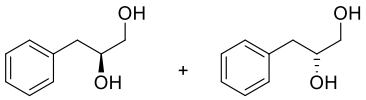
184 **182b**

Scheme 105 - Sharpless dihydroxylation of alkene 184

A small range of substituted alkenes were then used to synthesise their corresponding racemic mixture of diols with methanesulfonamide used as an additive for reactions involving non-terminal alkenes (Table 9).

Table 9 - Synthesis of a range of chiral diols from their parent alkenes using the Sharpless dihydroxylation reaction conditions



alkene	diol	yield %
 **184**	 **182b**[a]	84
 **185**	 **182i**	79
 **186**	 **182j**	62

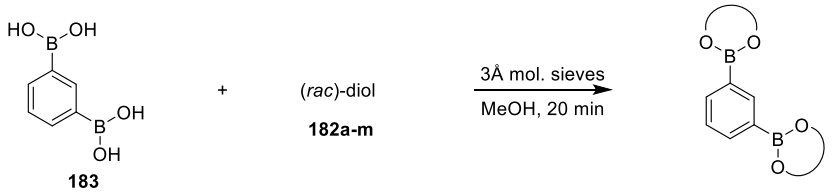
[a] $MeSO_2NH_2$ used only as an additive for reactions employing non-terminal alkenes as reagents.[213]

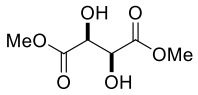
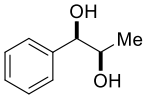
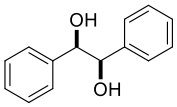
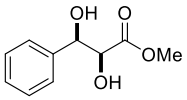
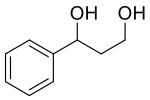
In all cases racemics mixture of the known chiral diols **182b,i,j** were successfully synthesised in good yields (62-84%) and characterised by ^{1}H NMR spectroscopy, mass spectrometry and the presence of a broad OH stretch in their IR spectrum.

4.2.2 Scope and Limitations of the Chiral Derivatization Protocol

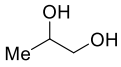
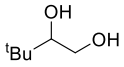
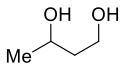
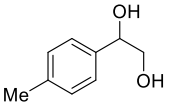
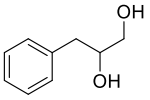
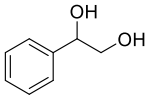
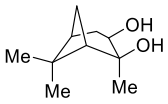
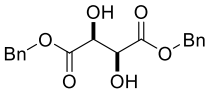
To investigate the scope and limitations of this simple protocol, our synthesized racemic diols **182b,i,j** and a range of commercially available racemic diols **182a,c-h,k-m** were derivatized with 1,3-phenyldiboronic acid **183** in methanol, with 3Å molecular sieves added to remove water and drive the equilibrium towards boronate ester formation (Table 10).

Table 10 - Reaction of 1,3-phenylboronic acid 183 with a range of functionalised chiral diols 182a-h



diol	diol
 **182a**	 **182b**
 **148c**	 **182d**
 **182e**	

e.e. successfully determined by ^{1}H NMR spectroscopic analysis under standard conditions

 **182f**	 **182g**
 **182h**	 **182i**
 **182j**	 **182k**
 **182l**	 **182m**

e.e. unsuccessfully determined by ^{1}H NMR spectroscopic analysis under standard conditions

These derivatization reactions gave their corresponding diastereomeric boronate esters **187/188a-m** in quantitative yield with their formation confirmed by ^{1}H NMR spectroscopic analysis in deuterated chloroform, and by the appearance of a single boronate resonance in their respective ^{11}B NMR spectrum. Analysis of the 500 MHz ^{1}H NMR spectrum of the resultant mixture of diastereomeric boronate esters **187/188a-m** revealed separation of diastereomeric resonances in a number of cases, particularly those diol substrates containing phenyl and ester functionalities (**182a-e)**. Unfortunately diastereomeric boronate esters derived from alkyl chain based diols **182f-h** showed no such splitting of the aryl proton of the core aryl template at its 2-position. All chiral diols containing vicinal stereocentres showed diastereomeric resonances for the aryl proton at the 2-position of the 1,3-phenyldiboronic acid fragment with sufficient baseline resolution for their enantiopurities to be determined except for diol **182l**. It was also seen that only dimethyl-DL-tartrate resulted in splitting of protons in the diol fragments of their diastereomeric boronate esters. In all other cases where splitting occurred only the proton at the 2-position of the aryl ring on the boronic acid fragment displayed baseline resolved diastereomeric resonances in their 500 MHz ^{1}H NMR spectra. Diastereomeric resonances were also seen in the ^{13}C NMR spectra for the derivatization products obtained from diols **182a,d,e,m** which meant that ^{13}C NMR spectroscopic analysis could be used to determine the enantiomeric excess of dibenzyl-DL-tartrate **182m** (Figure 47).

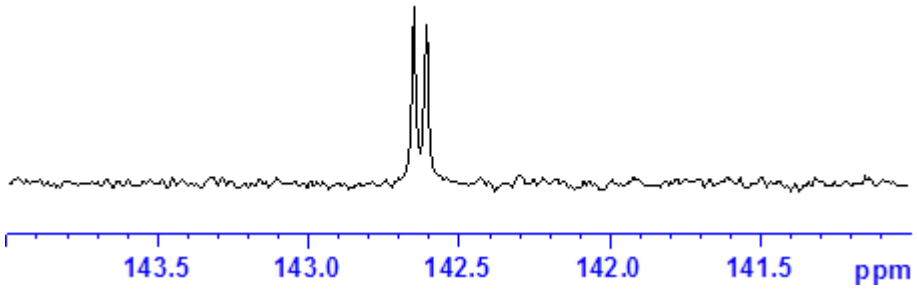


Figure 47 - Expansion of the aryl region of the 125 MHz ^{13}C NMR of the diastereomeric mixture formed from racemic dibenzyl-DL-tartrate 182m and 1,3-phenyldiboronic acid 183 showing splitting of the aryl carbon at 142.6 ppm

4.2.3 Attempted Improvements of Δδ Values

In an attempt to improve the splitting of these resonances and increase the usefulness of this protocol, samples were analysed of selected mixtures of diastereomeric *bis*-boronate esters using 700 MHz NMR spectroscopy (with thanks to Prof. David Smith at the University of York for analysing these samples for us), however the additional strength of the magnetic field showed no improvement for these substrates whose signals were not already split at 500 MHz. Advanced NMR experiments and processing techniques were also carried out which showed some improvement in the splitting of diastereomeric resonances for diols **182k,m**. We hypothesised that diastereomeric resonances were splitting in all cases, however, in some cases the Δδ values are very small, perhaps as small as 1 Hz and thus the broadness of the resonances in the ^{1}H NMR spectra cause the diastereomeric peaks to overlap. This broadening could perhaps be caused by remote coupling to other protons and in fact, upon close inspection of the ^{1}H NMR spectra, particularly for the aryl protons, small long range couplings were seen. In order to eliminate these coupling effects a proton decoupled (^{1}H{^{1}H}) experiment was acquired. It was found for diol **182m** that selective irradiation at 8.05 ppm with a low power pulse during acquisition removed these coupling effects causing a sharpening of the diastereomeric resonances at 8.47 ppm (Figure 48).

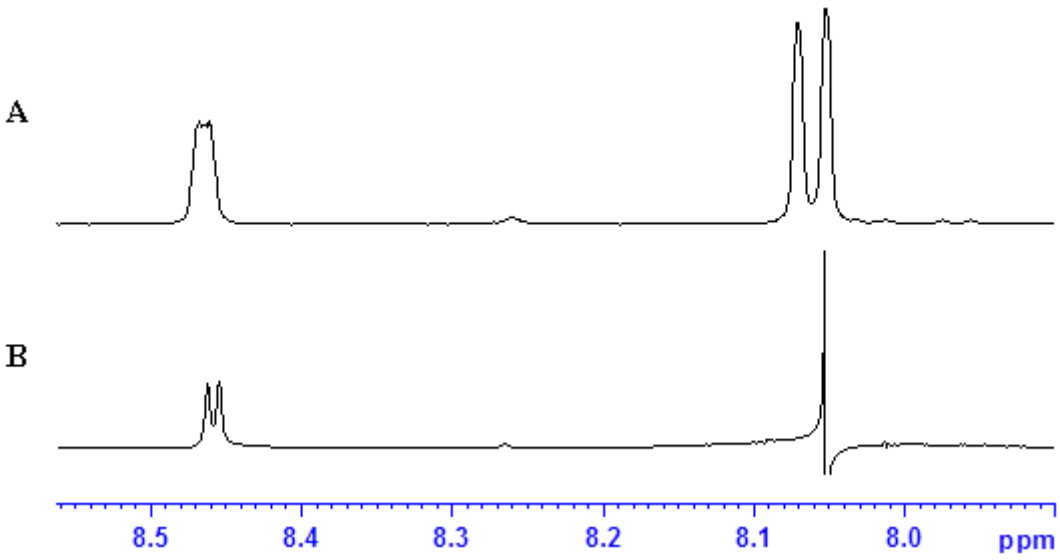


Figure 48 - Expansion of the aryl region of the 500 MHz ^{1}H NMR of the diastereomeric mixture formed from racemic dibenzyl-DL-tartrate 182m and 1,3-phenyldiboronic acid 183, showing the effect on splitting of the diastereomeric resonance at 8.47ppm from a standard ^{1}H NMR experiment (A) compared to a ^{1}H{^{1}H} experiment (B)

This experiment equalises the up or down spins of the particular resonance irradiated so no remote coupling was observed and thus sharper peaks are observed. The same experiment was also able to provide improvement to the Δδ value for the derivatization of **182k** (Figure 49).

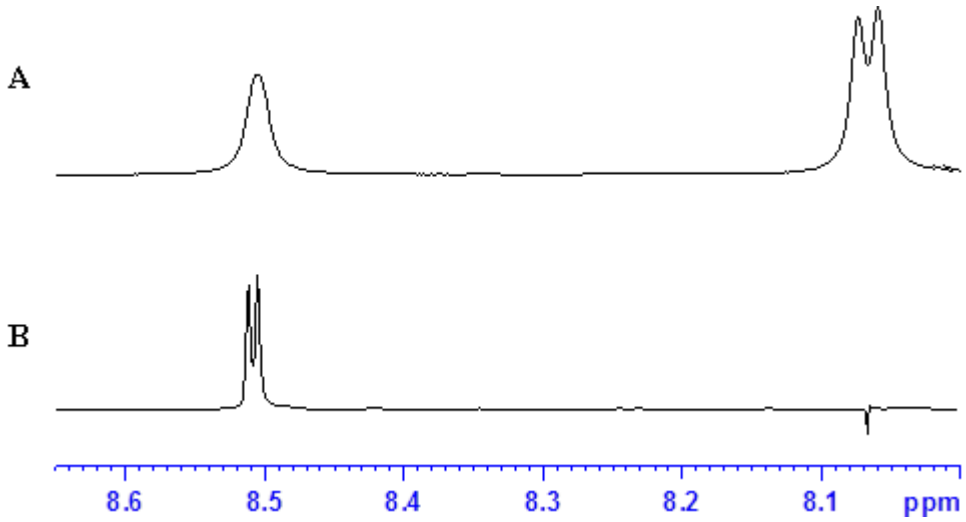


Figure 49 - Expansion of the aryl region of the 500 MHz ^{1}H NMR of the diastereomeric mixture formed from racemic 1-phenyl-1,2-ethanediol 182k and 1,3-phenyldiboronic acid 183, showing the effect on splitting of the diastereomeric resonance at 8.51ppm from a standard ^{1}H NMR experiment (A) compared to a ^{1}H{^{1}H} experiment (B)

Gaussian enhancement was also shown to be a useful processing technique for improving the splitting of diastereomeric resonances. This processing technique multiplies the raw FID signal obtained from the ^{1}H NMR acquisition by a Gaussian function which artificially enhances the signal in the middle of the FID. When the FID is then processed, this Gaussian enhancement gives the effect that the signal has been obtained over a longer time, sharpening the peaks and resulting in an increase in the amount of baseline separation (Figure 50).

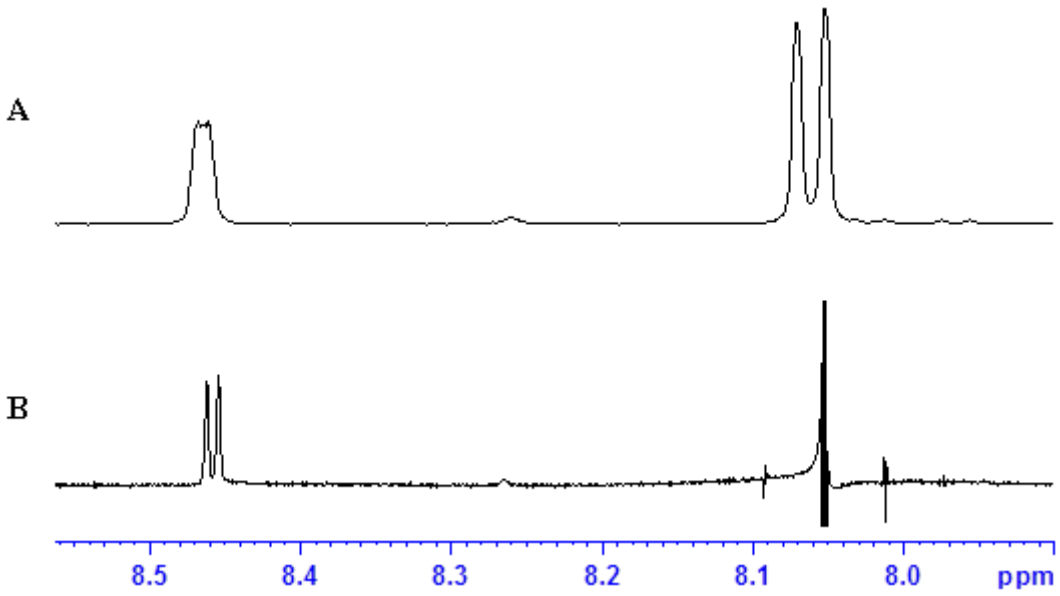


Figure 50 - Expansion of the aryl region of the 500 MHz ^{1}H NMR of the diastereomeric mixture formed from racemic dibenzyl-DL-tartrate 182m and 1,3-phenyldiboronic acid 183, showing the effect on splitting of the diastereomeric resonance at 8.47ppm of using standard processing (A) compared to processing using Gaussian enhancement of a ^{1}H{^{1}H} experiment (B)

Therefore, it has been shown that advanced NMR techniques can be successfully employed to improve the baseline separation of diastereomeric resonances for diols which only display partial separation in their ^{1}H NMR spectrum under standard conditions.

4.2.4 Scalemic Sampling Studies

In order to determine the accuracy of this protocol, scalemic samples of methyl-2,3-dihydroxy-3-phenylpropionate **182d** of 95%, 80% and 60% enantiomeric excess were derivatized with 1,3-phenyldiboronic acid **183** in methanol. Integration of the resultant ^{1}H NMR spectra showed that the integral of the diastereomeric resonances at δ 8.57 ppm and δ 8.59 ppm varied with diastereomeric excess (Figure 51).

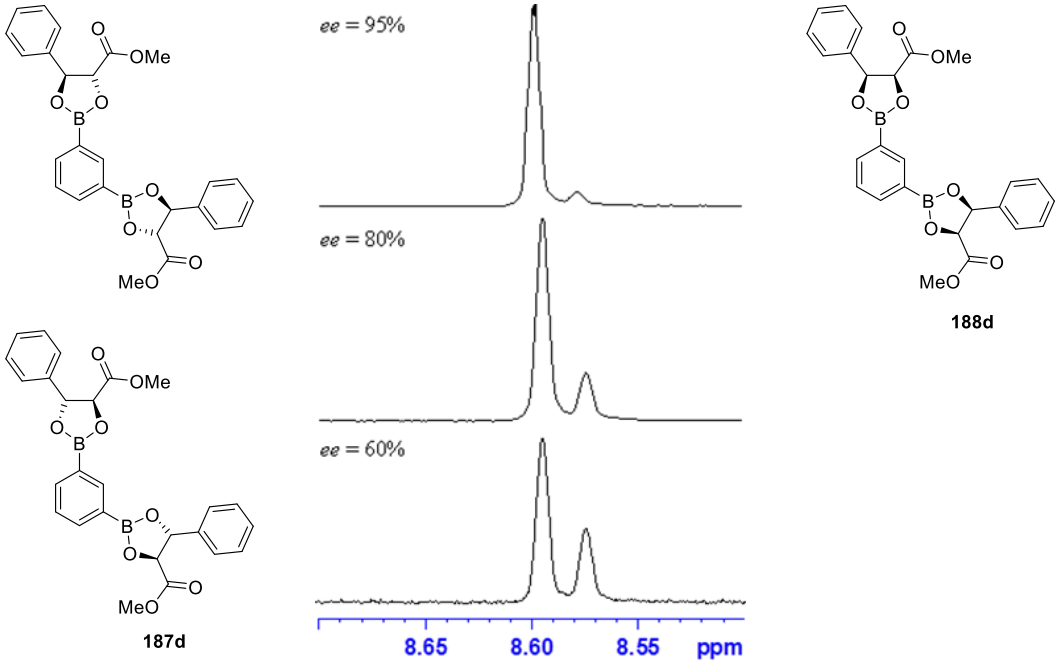


Figure 51 - Expansion of the diastereomeric aryl resonances at 8.58 ppm for the derivatization of diol 182d with 1,3-phenyldiboronic acid 183. Scalemic samples of diol 182d of 95%, 80% and 60% were employed

Using the calibration curve shown in Figure 46 it was determined that these samples had a measured enantiomeric excess of 94%, 78% and 58% respectively, showing excellent agreement with the known values of 95%, 80% and 60% *e.e.*. This scalemic sampling was also able to determine which resonance corresponded to the homochiral **187** and heterochiral **188** diastereomers. Therefore, it was determined that the most downfield resonance at 8.59 ppm was due to the homochiral diastereomer **187** and the upfield resonance of the pair (8.57 ppm) due to the heterochiral diastereomer **188** since, for all non-racemic samples the homochiral diastereomeric resonance will have the largest integral.

4.2.5 Molecular Modelling to Explain Differences in Diastereomeric Resonances

Molecular modelling software, Spartan, was used in an attempt to elucidate a model for why diastereomeric resonances are seen in the ^{1}H and ^{13}C NMR spectra of the derivatization products for only some of the diols investigated. Energy minimisation

and equilibrium geometry calculations using a semi-empirical (PM3) method were used to produce the lowest energy conformations of the heterochiral and homochiral boronate esters formed in the reaction between 1,3-phenyldiboronic acid **183** and 1-phenyl-1,3-propanediol **182e** (Figure 52).

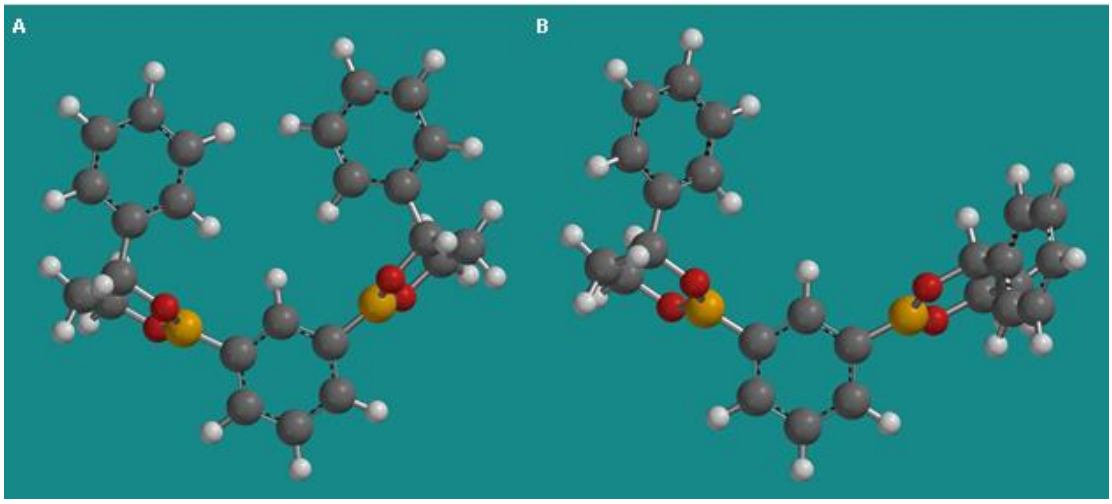


Figure 52 - Molecular modelling of the (*R*,*S*)-heterochiral (A) and (*R*,*R*)-homochiral (B) boronate ester conformers formed between 1,3-phenyldiboronic acid 183 and 1-phenyl-1,3-propanediol 182e

As can be seen from the two simple models in Figure 52, for the heterochiral model (A), the phenyl rings of the diol fragment point towards the aryl proton situated between the two boronate functionalities. The shielding effects of both of the phenyl rings cause a relative shift of its resonance to a higher δ value in the ^{1}H NMR spectrum. In the homochiral model, one of the phenyl rings points away from the aryl proton and as a consequence the shielding effects for this isomer are thus much less than for the heterochiral model resulting in a chemical shift to a lower δ value. This is consistent with the observation of diastereomeric resonances being observed when the reaction between 1,3-phenyldiboronic acid **183** and (*rac*)-1-phenyl-1,3-propanediol **182e** was analysed by 500 MHz ^{1}H NMR spectroscopy. In order to confirm whether this model might explain the larger Δδ values seen for certain diols, modelling was also performed on a diol that showed no splitting in its 500

MHz NMR spectrum. The same energy minimisation and equilibrium geometry calculations using a semi-empirical (PM3) method were performed on the heterochiral and homochiral boronate esters formed from reactions of 1,3-phenyldiboronic acid **183** and 1,3-butanediol **182h** (Figure 53).

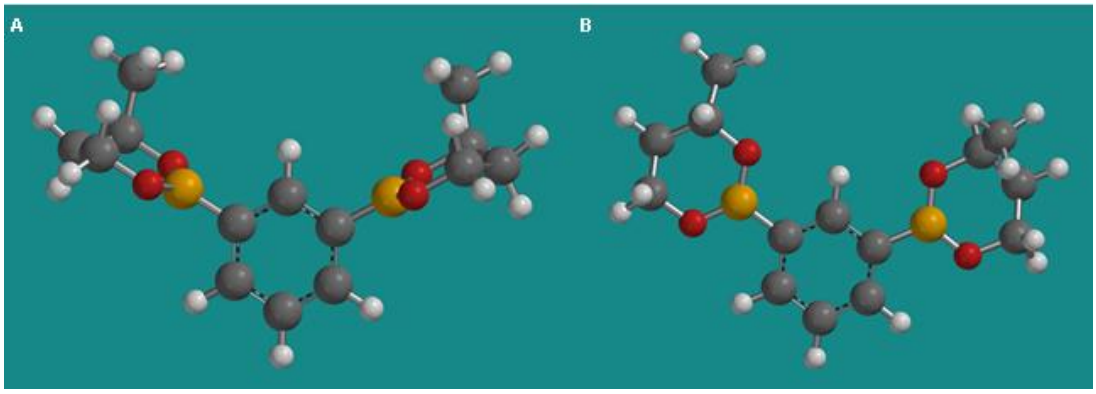


Figure 53 - Molecular modelling of the (*R*,*S*)-heterochiral (A) and (*R*,*R*)-homochiral (B) boronate ester conformers formed between 1,3-phenyldiboronic acid 183 and 1,3-butanediol 182h

The modelling of the 1,3-butanediol diboronate ester showed that, in the case of the heterochiral species, although the methyl groups of the diol fragment point towards the aryl proton between the two boronate ester units, they are not close enough to have any significant shielding effects on the proton. For the homochiral species, one methyl group points parallel to the aryl proton, whilst the other points away from the aryl ring. This arrangement would also cause no significant shielding effect on the aryl proton, and thus the difference in chemical shifts between the heterochiral and homochiral species is likely to be much smaller.

4.3 Conclusions

In conclusion, a new, simple protocol has been developed for the determination of the enantiomeric excess of chiral diols which the Horeau gambit to differentiate between heterochiral and homochiral diastereomers formed between a diol and an achiral bifunctional boronic acid template. This protocol has been shown to be successful for diols bearing anisotropically shielding groups adjacent to their diol functionalities, and molecular modelling has been used to rationalise the observed relative shift to higher δ value of their heterochiral diastereomers when compared to their homochiral diastereomers. In a number of cases diastereomeric resonances were seen in both the ^{1}H and ^{13}C NMR spectra of the derivatized diols, thus giving two sources for determination of their enantiomeric excess. For cases where $\Delta\delta$ values are small, alternative NMR spectroscopic experiments have been used to sharpen the diastereomeric resonances in the ^{1}H NMR spectrum of the mixture of derivatization products. Both commercially sourced diols and those synthesised racemically from their parent alkenes using Sharpless dihydroxylation reactions have been employed, and the accuracy of this new NMR protocol for determining enantiomeric excess has been determined using scalemic samples of known enantiomeric excess.

5 Experimental

5.1 General Experimental Details

All reagents and solvents used throughout this project were reagent grade unless otherwise reported and obtained from Acros Organics, Alfa Aesar, Fisher Scientific UK, Frontier Scientific Europe Ltd. or Sigma Aldrich Company Ltd. None of the reagents underwent further purification unless otherwise stated. All anhydrous solvents used were dried using an Innovative Technology PS-400-7 solvent purification system and all water was distilled. 4Å molecular sieves were activated by drying in an oven at 200 °C prior to use. All reactions were carried out at room temperature unless otherwise stated.

Flash chromatography was performed using chromatography grade silica, 60Å particle size 35-70 microns obtained from Fisher Scientific UK.

All ^{1}H NMR spectra were obtained at 500 MHz, 400 MHz or 300 MHz, ^{13}C NMR spectra obtained at 125 MHz, 100 MHz or 75 MHz and ^{11}B NMR spectra obtained at 96 MHz using a Bruker Avance 500, 400 or 300 spectrometer. All chemical shift values (δ) are reported in parts per million (ppm) and are referenced to the residual solvent peak. All coupling constants, *J*, are reported to the nearest 0.1 Hz. Multiplicities of observed peaks in the NMR spectra are denoted with the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sex, sextet; hep, heptet; dd, doublet of doublets; dq, doublet of quartets; m, multiplet; br, broad; hetero, heterochiral; homo, homochiral.

High resolution mass spectra were recorded on a Bruker Daltonics microTOF spectrometer with an electrospray source and external calibration. Masses were recorded were recorded in positive electrospray ionisation mode and were introduced by flow injection. Masses are accurate to 5 ppm and data was processed using DataAnalysis software available from Bruker Daltonics.

Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer, using a Universal ATR accessory for sampling, with only selected absorbances reported as ν in cm^{-1}.

Optical rotations were recorded on an Optical Activity Ltd AA-10 automatic polarimeter with a path length of 1 dm, concentrations (c) are quoted in g/100 mL.

All capillary melting points were measured using Stuart digital SMP10 melting point apparatus with 1 degree resolution.

X-ray crystallographic data was collected at 150K on a Nonius KappaCCD area detector diffractometer using Mo-Kα radiation (λ=0.71073 Å). All structures were solved by direct methods and refined on all *F2* data using SHELXL-97 suite of programs, with hydrogen atoms included in idealised positions and refined using the riding model.

5.2 General Procedures for Chapter 2

5.2.1 General Procedure 1: (*S*,*S*)-α-Amino Nitrile Hydrochloride Formation

In an adaptation to the literature procedure,[117,118] (*S*)-1-(4-methoxyphenyl)ethanamine (1.0 equiv.) was stirred in 1 M HCl in ether (1.0 equiv.) in ether to yield the amine hydrochloride salt as a white powder. The solvent was removed under reduced pressure and sodium cyanide was added (1.5 equiv.) in water. MeOH and the corresponding arylaldehyde (1.0 equiv) were added, and the mixture stirred for 16 hours. The reaction was diluted with water and the resulting solid collected *via* filtration and washed with *n*-hexane. If a single diastereomer was not precipitated from solution, the reaction mixture was extracted with CH_2Cl_2 and the organic layer dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was dissolved in ether and saturated methanolic HCl was added. The resultant white crystalline solid corresponding to the major (*S*,*S*)-α-

amino nitrile hydrochloride diastereomer was collected *via* filtration and washed with *n*-hexane.

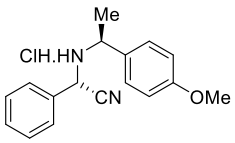
5.2.2 General Procedure 2: (*S*)-α-Arylglycine Hydrochloride Formation

The (*S*,*S*)-α-amino nitrile was treated with 6 M $HCl_{(aq)}$ (amount corresponding to a 0.1 M solution) and the resultant mixture heated at 90 °C for four hours. The reaction mixture was then cooled to room temperature and extracted with ether. The aqueous layer was concentrated under reduced pressure to give white/yellow solid. The crude material was suspended in $CDCl_3$ using a sonicator and filtered to yield the corresponding (*S*)-α-arylglycine hydrochloride as a white solid.

5.2.3 General Procedure 3: Determination of the Enantiomeric Excess of (*S*)-α-Arylglycine Hydrochlorides

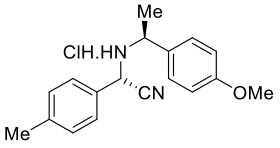
The α-arylglycine hydrochloride was converted to its respective methyl ester hydrochloride by heating them at reflux at 85 °C in 3 M $HCl_{(aq)}$ in methanol for 12 hours. The solvent was evaporated to give the methyl ester hydrochloride in a quantitative yield. This was subsequently treated with 2-formylphenylboronic acid (1.0 equiv), (*S*)-BINOL (1.1 equiv) and K_2CO_3 and stirred in $CDCl_3$ with 4 Å molecular sieves for 5 minutes. The resultant mixture was then filtered through a small pad of Celite to give a solution ready for ^1H NMR spectroscopic analysis.

5.3 Synthesis of Compounds in Chapter 2



(S)-2-(((S)-1-(4-methoxyphenyl)ethyl)amino)-2-phenylacetonitrile hydrochloride 122a

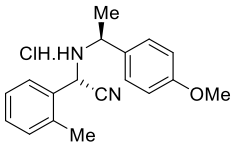
The title compound was prepared according to General Procedure 1 using (*S*)-1-(4-methoxyphenyl)ethanamine (0.44 mL, 3.0 mmol) which was stirred in 1 M HCl solution in ether (3 mL, 3.0 mmol) in ether (3 mL) for ten minutes to yield the equivalent hydrochloride salt as a white powder. The solvent was removed under reduced pressure and sodium cyanide (221 mg, 4.5 mmol) was added in 5 mL of water. Benzaldehyde (0.30 mL, 3.0 mmol) in methanol (5 mL) was added and the reaction stirred for 16 hours. The reaction mixture was diluted with water (10 mL) and after work up and recrystallization from ether and saturated methanolic HCl the α-amino nitrile **122a** (562 mg, 62%) was obtained as white needles. mp: 127-128 °C; $[\alpha]_D^{25}$ = -95 (*c* 0.525, $CHCl_3$); ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.49-7.46 (2H, m, Ar*H*), 7.42-7.34 (5H, m, Ar*H*), 6.93 (2H, d, J = 8.7 Hz, Ar*H*), 4.38 (1H, s, C*H*CN), 4.20 (1H, q, *J* = 6.5 Hz, C*H*CH_3), 3.82 (3H, s, CH_3O), 1.41 (3H, d, *J* = 6.5 Hz, CHCH_3); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 161.1, 134.9, 131.3, 130.8, 130.2, 129.6, 128.9, 115.4, 114.8, 59.3, 55.8, 50.7, 20.7; *m/z* (CI) 266 (M-HCl).



(S)-2-(((S)-1-(4-methoxyphenyl)ethyl)amino)-2-(p-tolyl)acetonitrile hydrochloride 122b

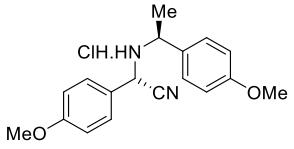
The title compound was prepared according to General Procedure 1 using (*S*)-1-(4-methoxyphenyl)ethanamine (0.44 mL, 3.0 mmol) which was stirred in 1 M HCl solution in ether (3 mL, 3.0 mmol) in ether (3 mL) for ten minutes to yield the equivalent hydrochloride salt as a white powder. The solvent was removed under reduced pressure and sodium cyanide (221 mg, 4.5 mmol) was added in 5 mL of water. *p*-Tolualdehyde (0.35 mL, 3.0 mmol) in methanol (5 mL) was added and the reaction stirred for 16 hours. The reaction mixture was diluted with water (10 mL) and after work up and recrystallization from ether and saturated methanolic HCl the α-amino nitrile **122b** (739 mg, 77%) was obtained as white needles. mp: 118-119 °C; $[\alpha]_D^{25}$ = -100 (*c* 0.510, $CHCl_3$); IR (film / cm^{-1}) ν = 3304 cm^{-1} (NH), 2228 (CN); ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.39-7.33 (4H, m, Ar*H*), 7.20 (2H, d, *J* = 8.0 Hz, Ar*H*), 6.92 (2H, d, J = 8.6 Hz, Ar*H*), 4.34 (1H, s, C*H*CN), 4.19 (1H, q, *J* = 6.5 Hz,

C*H*CH$_3$), 3.82 (3H, s, C*H*$_3$O), 2.35 (3H, s, ArC*H*$_3$), 1.40 (3H, d, *J* = 6.5 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 159.3, 138.9, 135.1, 132.5, 129.7, 128.2, 127.2, 119.3, 114.4, 56.3, 55.4, 52.1, 25.0, 21.3; *m/z* (EI) 265 (M-HCl-Me).



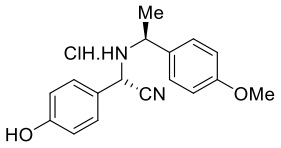
(S)-2-(((S)-1-(4-methoxyphenyl)ethyl)amino)-2-(o-tolyl)acetonitrile hydrochloride 122c

The title compound was prepared according to General Procedure 1 using (*S*)-1-(4-methoxyphenyl)ethanamine (0.44 mL, 3.0 mmol) which was stirred in 1 M HCl solution in ether (3 mL, 3.0 mmol) in ether (3 mL) for ten minutes to yield the equivalent hydrochloride salt as a white powder. The solvent was removed under reduced pressure and sodium cyanide (221 mg, 4.5 mmol) was added in 5 mL of water. *o*-Tolualdehyde (0.35 mL, 3.0 mmol) in methanol (5 mL) was added and the reaction stirred for 16 hours. The reaction mixture was diluted with water (10 mL) and after filtration the α-amino nitrile **122c** (570 mg, 60%) was obtained as white plates. mp: 129-132 °C; $[\alpha]_D^{25}$ = -189 (*c* 0.475, $CHCl_3$); IR (film / cm^{-1}) ν = 3338 cm^{-1} (NH), 2222 (CN); ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.57-7.55 (1H, m, Ar*H*), 7.38 (2H, d, *J* = 8.7 Hz, Ar*H*), 7.28-7.15 (3H, m, Ar*H*), 6.92 (2H, d, J = 8.6 Hz, Ar*H*), 4.39 (1H, s, C*H*CN), 4.20 (1H, q, *J* = 6.4 Hz, C*H*CH$_3$), 3.83 (3H, s, C*H*$_3$O), 2.14 (3H, s, ArC*H*$_3$), 1.40 (3H, d, *J* = 6.4 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 159.7, 136.7, 134.9, 133.8, 131.5, 129.5, 128.8, 127.7, 127.0, 119.5, 114.5, 56.7, 55.7, 50.6, 24.7, 19.0; *m/z* (CI) 265 (M-HCl-Me).



(S)-2-(4-methoxyphenyl)-2-(((S)-1-(4-methoxyphenyl)ethyl)amino)acetonitrile hydrochloride 122d

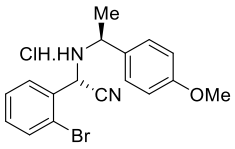
The title compound was prepared according to General Procedure 1 using (*S*)-1-(4-methoxyphenyl)ethanamine (0.44 mL, 3.0 mmol) which was stirred in 1 M HCl solution in ether (3 mL, 3.0 mmol) in ether (3 mL) for ten minutes to yield the equivalent hydrochloride salt as a white powder. The solvent was removed under reduced pressure and sodium cyanide (221 mg, 4.5 mmol) was added in 5 mL of water. *p*-Methoxybenzaldehyde (0.37 mL, 3.0 mmol) in methanol (5 mL) was added and the reaction stirred for 16 hours. The reaction mixture was diluted with water (10 mL) and after filtration the α-amino nitrile **122d** (871 mg, 87%) was obtained as a white solid. mp: 109-111 °C; $[\alpha]_D^{20}$ = -27.4 (*c* 0.475, MeOH); IR (film / cm^{-1}) ν = 3306 cm^{-1} (NH), 2227 (CN); ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.40-7.35 (4H, m, Ar*H*), 6.95-6.86 (4H, m, Ar*H*), 4.32 (1H, s, C*H*CN), 4.18 (1H, q, *J* = 6.6 Hz, C*H*CH_3), 3.82 (3H, s, CH_3O), 3.81 (3H, s, CH_3O), 1.40 (3H, d, *J* = 6.6 Hz, CHCH_3); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 160.1, 159.3, 135.1, 128.5, 128.2, 127.5, 119.3, 114.4, 56.3, 55.5, 55.4, 51.8, 24.9; HRMS (ES): *m/z* calculated for $C_{18}H_{21}N_2O_2$ [M + H]$^+$: 297.1603; found: 297.1605.



(S)-2-(4-hydroxyphenyl)-2-(((S)-1-(4-methoxyphenyl)ethyl)amino)acetonitrile hydrochloride 122e

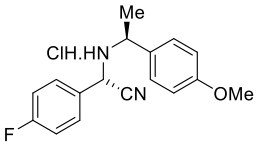
The title compound was prepared according to General Procedure 1 using (*S*)-1-(4-methoxyphenyl)ethanamine (0.44 mL, 3.0 mmol) which was stirred in 1 M HCl solution in ether (3 mL, 3.0 mmol) in ether (3 mL) for ten minutes to yield the equivalent hydrochloride salt as a white powder. The solvent was removed under reduced pressure and sodium cyanide (221 mg, 4.5 mmol) was added in 5 mL of water. *p*-Hydroxybenzaldehyde (0.37 g, 3.0 mmol) in methanol (5 mL) was added and the reaction stirred for 16 hours. The reaction mixture was diluted with water (10 mL) and after filtration the α-amino nitrile **122e** (819 mg, 86%) was obtained as a white solid. mp: 132-134 °C; $[\alpha]_D^{20}$ = -40.7 (*c* 0.590, MeOH); IR (film / cm^{-1}) ν = 3261 cm^{-1} (NH), 2228 (CN); ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.37 (2H, app d, *J* = 8.7 Hz, Ar*H*), 7.30 (2H, app d, *J* = 8.4 Hz, Ar*H*), 6.92 (2H, app d, J = 8.7 Hz, Ar*H*),

6.81 (2H, app d, J = 8.7 Hz, Ar*H*), 4.30 (1H, s, C*H*CN), 4.16 (1H, q, *J* = 6.4 Hz, C*H*CH$_3$), 3.82 (3H, s, C*H*$_3$O), 1.40 (3H, d, *J* = 6.4 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 159.3, 156.4, 135.0, 128.7, 128.2, 127.3, 119.3, 115.9, 114.4, 56.3, 55.5, 51.8, 24.9; HRMS (ES): *m/z* calculated for $C_{17}H_{18}N_2NaO_2$ $[M + Na]^+$: 305.1266; found: 305.1255.



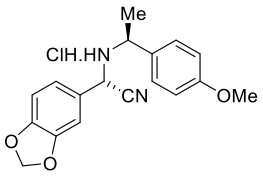
(*S*)-2-(2-bromophenyl)-2-(((*S*)-1-(4-methoxyphenyl)ethyl)amino)acetonitrile hydrochloride *122f*

The title compound was prepared according to General Procedure 1 using (*S*)-1-(4-methoxyphenyl)ethanamine (0.44 mL, 3.0 mmol) which was stirred in 1 M HCl solution in ether (3 mL, 3.0 mmol) in ether (3 mL) for ten minutes to yield the equivalent hydrochloride salt as a white powder. The solvent was removed under reduced pressure and sodium cyanide (221 mg, 4.5 mmol) was added in 5 mL of water. 2-Bromobenzaldehyde (0.35 mL, 3.0 mmol) in methanol (5 mL) was added and the reaction stirred for 16 hours. The reaction mixture was diluted with water (10 mL) and after filtration the α-amino nitrile **122f** (662 mg, 58%) was obtained as white plates. mp: 117-119 °C; $[\alpha]_D^{25}$ (*d.e.*= 90%) = -166 (*c* 0.525, $CHCl_3$); IR (film / cm^{-1}) ν = 3333 cm^{-1} (NH), 2228 (CN); ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.63-7.56 (2H, m, Ar*H*), 7.42-7.35 (3H, m, Ar*H*), 7.28-7.21 (1H, m, Ar*H*), 6.93-6.90 (2H, m, Ar*H*), 4.66 (1H, s, C*H*CN), 4.18 (1H, q, *J* = 6.6 Hz, C*H*CH$_3$), 3.83 (3H, s, C*H*$_3$O), 1.74 (1H, br s, N*H*), 1.42 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 159.7, 135.2, 134.5, 134.1, 131.0, 129.7, 128.9, 128.6, 123.7, 118.9, 114.4, 56.7, 55.7, 52.8, 24.9; *m/z* (CI) 346 (M^+) 344 (M^+).



(S)-2-(4-fluorophenyl)-2-(((S)-1-(4-methoxyphenyl)ethyl)amino)acetonitrile hydrochloride 122g

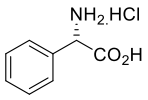
The title compound was prepared according to General Procedure 1 using (*S*)-1-(4-methoxyphenyl)ethanamine (0.44 mL, 3.0 mmol) which was stirred in 1 M HCl solution in ether (3 mL, 3.0 mmol) in ether (3 mL) for ten minutes to yield the equivalent hydrochloride salt as a white powder. The solvent was removed under reduced pressure and sodium cyanide (221 mg, 4.5 mmol) was added in 5 mL of water. 4-Fluorobenzaldehyde (0.32 mL, 3.0 mmol) in methanol (5 mL) was added and the reaction stirred for 16 hours. The reaction mixture was diluted with water (10 mL) and after work up and recrystallization from ether and saturated methanolic HCl the α-amino nitrile **122g** (674 mg, 70%) was obtained as white needles. mp: 137-138 °C; $[\alpha]_D^{25}$ = -53 (*c* 0.510, MeOH); ^{1}H NMR (300 MHz; $(CD_3)_2SO$) δ_H 7.66-7.58 (2H, m, Ar*H*), 7.39 (2H, d, *J* = 8.6 Hz, Ar*H*), 7.23-7.17 (2H, m, Ar*H*), 6.87 (2H, d, *J* = 8.6 Hz, Ar*H*), 5.19 (1H, s, C*H*CN), 4.16 (1H, q, *J* = 6.5 Hz, C*H*CH_3), 3.64 (3H, s, CH_3O), 1.49 (3H, d, *J* = 6.5 Hz, CHCH_3); ^{13}C NMR (75 MHz; $(CD_3)_2SO$) δ_C 159.7, 132.1, 129.8, 129.4, 128.8, 124.3, 116.0, 114.5, 114.2, 56.8, 55.2, 48.2, 20.3; *m/z* (CI) 284 (M - HCl).



(S)-2-(benzo[d][1,3]dioxol-5-yl)-2-(((S)-1-(4-methoxyphenyl)ethyl)amino)acetonitrile hydrochloride 122h

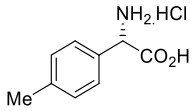
The title compound was prepared according to General Procedure 1 using (*S*)-1-(4-methoxyphenyl)ethanamine (0.44 mL, 3.0 mmol) which was stirred in 1 M HCl solution in ether (3 mL, 3.0 mmol) in ether (3 mL) for ten minutes to yield the equivalent hydrochloride salt as a white powder. The solvent was removed under

reduced pressure and sodium cyanide (221 mg, 4.5 mmol) was added in 5 mL of water. Piperonal (0.45 mL, 3.0 mmol) in methanol (5 mL) was added and the reaction stirred for 16 hours. The reaction mixture was diluted with water (10 mL) and after work up and recrystallization from ether and saturated methanolic HCl the α-amino nitrile **122h** (558 mg, 54%) was obtained as a white solid. mp: 116-119 °C; $[\alpha]_D^{22}$ = -60 (*c* 0.550, $CHCl_3$); IR (film / cm^{-1}) ν = 3032 cm^{-1} (NH), 2049 (CN); ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.64 (2H, d, *J* = 8.7 Hz, Ar*H*), 7.24-7.22 (1H, m, Ar*H*), 7.01-6.79 (4H, m, Ar*H*), 5.91 (2H, s, CH_2), 4.57 (1H, s, C*H*CN), 4.41 (1H, q, *J* = 6.8 Hz, C*H*CH_3), 3.84 (3H, s, CH_3O), 1.66 (3H, d, *J* = 6.4 Hz, CHCH_3); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 160.9, 150.1, 150.0, 148.3, 130.0, 129.8, 125.2, 124.6, 115.1, 114.9, 110.7, 108.8, 102.0, 58.9, 55.5, 50.3, 20.6; HRMS (ES): *m/z* calculated for $C_{18}H_{19}N_2O_3$ $[M + H]^+$: 311.1396; found: 311.1382.



(S)-2-amino-2-phenylacetic acid hydrochloride 124a

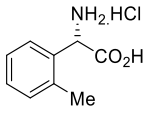
The title compound was prepared according to General Procedure 2 using α-amino nitrile **122a** (124 mg, 0.47 mmol) and 5 mL of 6 M $HCl_{(aq)}$. α-Arylglycine **124a** (53 mg, 60%) was obtained as a white solid. $[\alpha]_D^{20}$ = +152 (*c* 0.100, 1 M HCl); ^{1}H NMR (400 MHz; D_2O) δ_H 7.47-7.42 (5H, m, Ar*H*), 5.07 (1H, s, C*H*CO_2H); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 171.2, 131.9, 130.2, 129.7, 128.1, 56.9; *m/z* (CI) 152 (M - HCl).



(S)-2-amino-2-(p-tolyl)acetic acid hydrochloride 124b

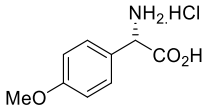
The title compound was prepared according to General Procedure 2 using α-amino nitrile **122b** (150 mg, 0.53 mmol) and 5 mL of 6 M $HCl_{(aq)}$. α-Arylglycine **124b** (60 mg, 56%) was obtained as a white solid. $[\alpha]_D^{20}$ = +70 (*c* 0.100, H_2O); IR (film / cm^{-1}) ν = 2976 cm^{-1} (br, NH), 2880 (br, OH), 1727 (C=O); ^{1}H NMR (300 MHz; D_2O) δ_H 7.29 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.26 (2H, d, *J* = 8.5 Hz, Ar*H*), 5.02 (1H, s,

C*H*CO_2H), 2.28 (3H, s, CH_3); ^{13}C NMR (75 MHz; D_2O) δ_C 171.1, 140.8, 130.1, 128.8, 128.0, 56.6, 20.3; HRMS (ES): *m/z* calculated for $C_9H_{12}NO_2$ $[M + H]^+$: 166.0868; found: 166.0870.



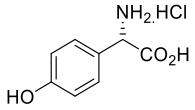
(S)-2-amino-2-(o-tolyl)acetic acid hydrochloride 124c

The title compound was prepared according to General Procedure 2 using α-amino nitrile **122c** (300 mg, 1.07 mmol) and 11 mL of 6 M $HCl_{(aq)}$. α-Arylglycine **124c** (173 mg, 80%) was obtained as a white solid. $[\alpha]_D^{25}$ = +90 (*c* 0.100, 5 M HCl); ^{1}H NMR (300 MHz; D_2O) δ_H 7.41-7.20 (4H, m, Ar*H*), 5.05 (1H, s, C*H*CO_2H), 2.04 (3H, s, CH_3); ^{13}C NMR (75 MHz; D_2O) δ_C 170.8, 137.4, 131.5, 130.3, 129.8, 127.1, 126.8, 53.1, 18.8; *m/z* (CI) 166 (M - Cl).



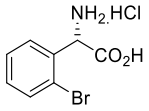
(S)-2-amino-2-(4-methoxyphenyl)acetic acid hydrochloride 124d

The title compound was prepared according to General Procedure 2 using α-amino nitrile **122d** (210 mg, 0.70 mmol) and 7 mL of 6 M $HCl_{(aq)}$. α-Arylglycine **124d** (79 mg, 52%) was obtained as a white solid. $[\alpha]_D^{22}$ = +41.7 (*c* 0.120, H_2O); IR (film / cm^{-1}) ν = 2969 (OH), 1733 (C=O); ^{1}H NMR (300 MHz; D_2O) δ_H 7.38 (2H, app d, *J* = 8.9 Hz, Ar*H*), 7.03 (2H, app d, *J* = 8.9 Hz, Ar*H*), 4.99 (1H, s, C*H*CO_2H), 3.81 (3H, s, CH_3O); ^{13}C NMR (75 MHz; D_2O) δ_C 160.4, 130.0, 124.8, 115.3, 56.7, 55.7; HRMS (ES): *m/z* calculated for $C_9H_{12}NO_3$ $[M + H]^+$: 182.0817; found: 182.0809.



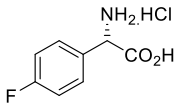
(S)-2-amino-2-(4-hydroxyphenyl)acetic acid hydrochloride 124e

The title compound was prepared according to General Procedure 2 using α-amino nitrile **122e** (200 mg, 0.70 mmol) and 7 mL of 6 M $HCl_{(aq)}$. α-Arylglycine **124e** (116 mg, 81%) was obtained as a white solid. $[\alpha]_D^{22}$ = +58.5 (*c* 0.205, H_2O); IR (film / cm^{-1}) ν = 3000 (OH), 1728 (C=O); ^{1}H NMR (300 MHz; D_2O) δ_H 7.31 (2H, app d, *J* = 8.6 Hz, Ar*H*), 6.91 (2H, app d, *J* = 8.6 Hz, Ar*H*), 5.04 (1H, s, C*H*CO_2H); ^{13}C NMR (75 MHz; D_2O) δ_C 171.7, 157.4, 130.2, 123.9, 116.6, 56.6; HRMS (ES): *m/z* calculated for $C_8H_{10}NO_3$ $[M + H]^+$: 168.0661; found: 168.0643.



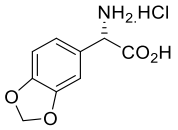
(S)-2-amino-2-(2-bromophenyl)acetic acid hydrochloride 124f

The title compound was prepared according to General Procedure 2 using α-amino nitrile **122f** (246 mg, 0.71 mmol) and 8 mL of 6 M $HCl_{(aq)}$. α-Arylglycine **124f** (151 mg, 80%) was obtained as a white solid. $[\alpha]_D^{25}$ = +90 (*c* 0.100, 1 M HCl); IR (film / cm^{-1}) ν = 3409 (OH), 1747 (C=O); ^{1}H NMR (300 MHz; D_2O) δ_H 7.64 (1H, d, *J* = 7.7 Hz, Ar*H*), 7.38-7.33 (2H, m, Ar*H*), 7.31-7.25 (1H, m, Ar*H*), 5.45 (1H, s, C*H*CO_2H); ^{13}C NMR (75 MHz; D_2O) δ_C 169.7, 133.0, 131.2, 130.5, 129.0, 128.0, 123.1, 55.5; *m/z* (CI) 232 (M - HCl).



(S)-2-amino-2-(4-fluorophenyl)acetic acid hydrochloride 124g

The title compound was prepared according to General Procedure 2 using α-amino nitrile **122g** (77 mg, 0.24 mmol) and 3 mL of 6 M $HCl_{(aq)}$. α-Arylglycine **124g** (31 mg, 63%) was obtained as a white solid. $[\alpha]_D^{22}$ = +132 (*c* 0.100, 1 M HCl); ^{1}H NMR (300 MHz; D_2O) δ_H 7.39-7.34 (2H, m, Ar*H*), 7.10 (2H, app t, *J* = 8.7 Hz, Ar*H*), 5.05 (1H, s, C*H*CO_2H); ^{13}C NMR (75 MHz; D_2O) δ_C 170.7, 163.3, 130.5, 127.6, 116.7, 56.1; *m/z* (CI) 170 (M - Cl).



(S)-2-amino-2-(benzo[d][1,3]dioxol-5-yl)acetic acid hydrochloride 124h

The title compound was prepared according to General Procedure 2 using α-amino nitrile **122h** (275 mg, 0.79 mmol) and 8 mL of 6 M $HCl_{(aq)}$. α-Arylglycine **124h** (118 mg, 64%) was obtained as a white solid. $[\alpha]_D^{20}$ = +70 (*c* 0.100, H_2O); IR (film / cm^{-1}) ν = 2976 (br, NH), 2880 (br, OH), 1727 (C=O); ^{1}H NMR (300 MHz; D_2O) δ_H 7.01-6.94 (3H, m, Ar*H*), 6.03 (2H, s, CH_2), 5.07 (1H, s, C*H*CO_2H); ^{13}C NMR (75 MHz; D_2O) δ_C 171.6, 149.0, 148.4, 125.7, 123.0, 109.5, 108.4, 102.2, 57.0; HRMS (ES): *m/z* calculated for $C_9H_{10}NO_4$ $[M + H]^+$: 196.0610; found: 196.0610.

5.4 General Procedures for Chapter 3

5.4.1 General Procedure 4: Chiral Hydroxylamine Formation

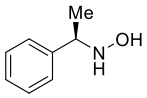
Chiral hydroxylamines **135a-h** were prepared according to adaptation of the general method of Wovkulich and Uskoković.[133] $MgSO_4$ (2.0 g) and *p*-anisaldehyde (1.0 equiv.) was added to a solution of the corresponding chiral amine (1.0 g, 1.0 equiv.) in MeOH (25 mL). The mixture was stirred for 24 hours, filtered and the solvent evaporated under reduced pressure. The residue was then dissolved in anhydrous CH_2Cl_2 (5 mL), cooled to 0 °C and a solution of *m*-chloroperoxybenzoic acid (70%, 1.2 equiv.) in anhydrous CH_2Cl_2 (30 mL) added dropwise. The reaction was stirred for 1 hour at 0 °C, warmed to room temperature and stirred for a further 3 hours. The resultant white suspension was filtered, neutralized with saturated aqueous $NaHCO_3$ (20 mL) and washed with brine (20 mL). The organic layer was dried over $MgSO_4$ and the solvent evaporated under reduced pressure to yield an oxaziridine intermediate. The crude oxaziridine was subsequently dissolved in anhydrous MeOH (20 mL) and hydroxylamine hydrochloride (2.0 equiv.) added in a single portion and the resultant solution then stirred overnight. $CHCl_3$ (20 mL) was then

added to precipitate unreacted hydroxylamine hydrochloride, the solution was filtered and the solvent evaporated. Water (20 mL) and Et_2O (20 mL) were added to the residue and the acidic aqueous layer then extracted with Et_2O (10 x 20 mL), until all nonpolar substances had been removed (checked by TLC). The aqueous layer was saturated with $NaHCO_3$ and extracted with Et_2O (3 x 20 mL). The combined organic layers were then dried over $MgSO_4$ and the solvent evaporated under reduced pressure to yield a hydroxylamine **135a-h** that was purified by recrystallization from 1:4 $CHCl_3$/hexane.

5.4.2 General Procedure 5: Determination of the Enantiomeric Excess of Chiral Hydroxylamines

To a solution of hydroxylamine **135a-h** (30 mg) dissolved in $CDCl_3$ (2 mL), 2-formylphenylboronic acid (1 equiv.), (*rac*)-BINOL (1.1 equiv.) and Cs_2CO_3 (1.1 equiv.) were added, $MgSO_4$ was then added and the suspension stirred for 15 minutes at room temperature, before filtering and acquiring a 500 MHz ^{1}H NMR spectrum.

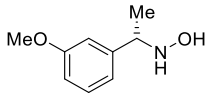
5.5 Synthesis of Compounds in Chapter 3



(R)-N-(1-phenylethyl)hydroxylamine 135a

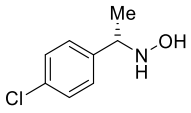
The title compound was prepared according to General Procedure 4 using (*R*)-α-methylbenzylamine (1.05 mL, 8.25 mmol), *p*-anisaldehyde (1.00 mL, 8.25 mmol), *m*-chloroperoxybenzoic acid (3.42 g, 9.90 mmol, 70%) and hydroxylamine hydrochloride (1.15 g, 16.50 mmol) to afford hydroxylamine **135a** as an off white solid (422 mg, 54%). mp: 96-97 °C; $[\alpha]_D^{22}$ = +37.0 (*c* 2.0, CH_2Cl_2); (Lit (-43.5, *c* 1.0, CH_2Cl_2 for (*S*)-1a)[156]; IR (film / cm^{-1}) ν = 3134 cm^{-1} (OH); ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.28-7.19 (5H, m, Ar*H*), 5.14 (2H, br s, N*H*O*H*), 4.06 (1H, q, *J* = 6.7

Hz, C*H*), 1.33 (3H, d, *J* = 6.7 Hz, CH_3); ^{13}C NMR (75 MHz; $CDCl_3$): δ_C = 142.2 (Ar*C*CHCH$_3$), 128.6 (Ar*C*HCHC), 127.7 (Ar*C*HCCH), 127.2 (Ar*C*H(CH)$_2$CCH), 61.8 (*C*HCH$_3$), 19.4 (*C*H$_3$); HRMS (ES): *m/z* calculated for $C_8H_{12}NO$ $[M + H]^+$: 138.0919; found: 138.0924.



(S)-N-(1-(3-methoxyphenyl)ethyl)hydroxylamine 135b

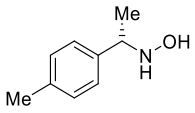
The title compound was prepared according to General Procedure 4 using (*S*)-3-methoxy-α-methylbenzylamine (0.98 mL, 6.61 mmol), *p*-anisaldehyde (0.81 mL, 6.61 mmol), *m*-chloroperoxybenzoic acid (2.74 g, 7.94 mmol, 70%) and hydroxylamine hydrochloride (0.92 g, 13.22 mmol) to afford hydroxylamine **135b** as a white solid (432mg, 55%). mp 60-61 °C; $[\alpha]_D^{22}$ = -40.0 (*c* 2.0, CH_2Cl_2); IR (film / cm^{-1}) ν = 3134 cm^{-1} (OH); ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.25 (1H, t, *J* = 7.6 Hz, Ar*H*), 6.93-6.85 (2H, m, Ar*H*), 6.80 (1H, d, *J* = 7.5 Hz, Ar*H*), 5.78 (2H, br s, N*H*O*H*), 4.08 (1H, q, *J* = 6.7 Hz, C*H*), 3.80 (3H, s, CH_3O), 1.38 (3H, d, *J* = 6.7 Hz, CH_3); ^{13}C NMR (75 MHz; $CDCl_3$): δ_C = 159.8, 144.0, 129.6, 119.4, 112.9, 112.8, 61.8, 55.2, 19.5; HRMS (ES): *m/z* calculated for $C_8H_{14}NO_2$ $[M + H]^+$: 168.1025; found: 168.1029.



(S)-N-(1-(4-chlorophenyl)ethyl)hydroxylamine 135c

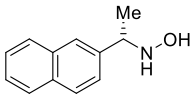
The title compound was prepared according to General Procedure 4 using (*S*)-4-chloro-α-methylbenzylamine (0.90 mL, 6.43 mmol), *p*-anisaldehyde (0.78 mL, 6.43 mmol), *m*-chloroperoxybenzoic acid (2.66 g, 7.71 mmol, 70%) and hydroxylamine hydrochloride (0.89 g, 12.85 mmol) to afford hydroxylamine **135c** as white needles (478 mg, 62%). mp 86-87 °C; $[\alpha]_D^{22}$ = -47.0 (*c* 2.0, CH_2Cl_2); IR (film / cm^{-1}) ν = 3163 cm^{-1} (OH); ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.28 (2H, d, *J* = 7.5 Hz, Ar*H*), 7.23 (2H, d, *J* = 7.5 Hz, Ar*H*), 5.38 (2H, br s, N*H*O*H*), 4.08 (1H, q, *J* = 6.7 Hz, C*H*),

1.35 (3H, d, *J* = 6.7 Hz, C*H*$_3$); ^{13}C NMR (75 MHz; $CDCl_3$): δ_C = 140.6, 133.3, 129.1, 128,3, 61.1, 19.1; HRMS (ES): *m/z* calculated for $C_8H_{11}ClNO$ $[M + H]^+$: 172.0529; found: 172.0534.



(S)-N-(1-(p-tolyl)ethyl)hydroxylamine 135d

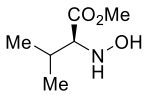
The title compound was prepared according to General Procedure 4 using (*S*)-α,4-dimethylbenzylamine (1.09 mL, 7.40 mmol), *p*-anisaldehyde (0.90 mL, 7.40 mmol), *m*-chloroperoxybenzoic acid (3.06 g, 8.88 mmol, 70%) and hydroxylamine hydrochloride (1.03 g, 14.79 mmol) to afford hydroxylamine **135d** as a pale brown solid (238 mg, 38%). mp 79-81 °C; $[\alpha]_D^{22}$ = -41.0 (*c* 2.0, CH_2Cl_2); IR (film / cm^{-1}) ν = 3144 cm^{-1} (OH); ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.22 (2H, d, *J* = 7.5 Hz, Ar*H*), 7.16 (2H, d, *J* = 7.5 Hz, Ar*H*), 5.78 (2H, br s, N*H*O*H*), 4.08 (1H, q, *J* = 6.6 Hz, C*H*), 2.34 (3H, s, ArC*H*$_3$), 1.38 (3H, d, *J* = 6.6 Hz, C*H*$_3$); ^{13}C NMR (75 MHz; $CDCl_3$): δ_C = 139.2, 137.3, 129.3, 127.1, 61.5, 21.1, 19.4; HRMS (ES): *m/z* calculated for $C_9H_{14}NO$ $[M + H]^+$: 152.1075; found: 152.1082.



(S)-N-(1-(naphthalen-2-yl)ethyl)hydroxylamine 135e

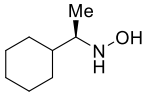
The title compound was prepared according to General Procedure 4 using (*S*)-1-(2-naphthyl)ethylamine (1.00 g, 5.84 mmol), *p*-anisaldehyde (0.71 mL, 5.84 mmol), *m*-chloroperoxybenzoic acid (2.42 g, 6.42 mmol, 70%) and hydroxylamine hydrochloride (0.81 g, 11.68 mmol) to afford hydroxylamine **135e** as a pale yellow solid (210 mg, 32%). mp 101-102 °C; $[\alpha]_D^{22}$ = -48.0 (*c* 2.0, CH_2Cl_2); IR (film / cm^{-1}) ν = 3162 cm^{-1} (OH); ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.80-7.83 (3H, m, Ar*H*), 7.77 (1H, s, Ar*H*), 7.45-7.48 (3H, m, Ar*H*), 5.08 (2H, br s, N*H*O*H*), 4.29 (1H, q, *J* = 6.7 Hz, C*H*), 1.47 (3H, d, *J* = 6.7 Hz, C*H*$_3$); ^{13}C NMR (75 MHz; $CDCl_3$): δ_C =

138.8, 133.3, 133.1, 128.4, 127.9, 127.7, 126.4, 126.2, 126.0, 125.1, 61.9, 19.2; HRMS (ES): *m/z* calculated for $C_{12}H_{14}NO$ $[M + H]^+$: 188.1075; found: 188.1068.



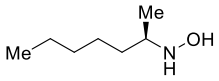
methyl hydroxy-L-valinate 135f

The title compound was prepared according to General Procedure 4 using (*L*)-valine methylester (1.00 g, 7.62 mmol), *p*-anisaldehyde (0.93 mL, 7.62 mmol), *m*-chloroperoxybenzoic acid (2.24 g, 9.15 mmol, 70%) and hydroxylamine hydrochloride (1.05 g, 15.25 mmol) to afford hydroxylamine **135f** as a white solid (351 mg, 46%). mp 59-61 °C; $[\alpha]_D^{22}$ = -10.0 (*c* 2.0, CH_2Cl_2); (Lit (-15.5, *c* 1.0, CH_2Cl_2)[157]; IR (film / cm^{-1}) ν = 3178 cm^{-1} (OH); ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 5.92 (2H, br s, N*H*O*H*), 3.77 (3H, s, C*H*$_3$O), 3.47 (1H, d, *J* = 6.7 Hz, C*H*NH), 1.91 (1H, m, C*H*CH$_3$), 0.96 (6H, t, *J* = 6.8 Hz, C*H*$_3$); ^{13}C NMR (75 MHz; $CDCl_3$): δ_C = 173.9, 71.2, 51.9, 29.0, 19.3, 19.2; HRMS (ES): *m/z* calculated for $C_6H_{14}NO_3$ $[M + H]^+$: 148.0974; found: 148.0988.



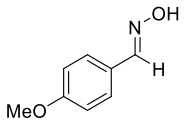
(R)-N-(1-cyclohexylethyl)hydroxylamine 135g

The title compound was prepared according to General Procedure 4 using (*R*)-cyclohexylethylamine (1.17 mL, 7.86 mmol), *p*-anisaldehyde (0.96 mL, 7.86 mmol), *m*-chloroperoxybenzoic acid (3.26 g, 9.43 mmol, 70%) and hydroxylamine hydrochloride (1.09 g, 15.71 mmol) to afford hydroxylamine **135g** as white needles (549 mg, 65%). mp 82 °C; $[\alpha]_D^{22}$ = -4.0 (*c* 2.0, CH_2Cl_2); IR (film / cm^{-1}) ν = 3197 cm^{-1} (OH); ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 5.48 (2H, br s, N*H*O*H*), 2.74 (1H, quin, *J* = 6.3 Hz, C*H*NH), 1.60-1.70 (5H, m, C*H*$_2$), 1.36-1.48 (1H, m, C*H*), 1.07-1.23 (3H, m, C*H*$_2$), 0.99 (3H, d, *J* = 6.6 Hz, C*H*$_3$), 0.86-0.95 (2H, m, C*H*$_2$); ^{13}C NMR (75 MHz; $CDCl_3$): δ_C = 61.8, 40.0, 29.9, 28.1, 26.5, 14.4; HRMS (ES): *m/z* calculated for $C_8H_{17}NO$ $[M + H]^+$: 144.1383; found: 144.1389.



(R)-N-(heptan-2-yl)hydroxylamine 135h

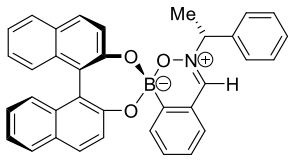
The title compound was prepared according to General Procedure 4 using (*R*)-2-aminoheptane (1.31 mL, 8.68 mmol), *p*-anisaldehyde (1.06 mL, 8.68 mmol), *m*-chloroperoxybenzoic acid (3.60 g, 10.41 mmol, 70%) and hydroxylamine hydrochloride (1.21 g, 17.36 mmol) to afford hydroxylamine **135h** as a white solid (190 mg, 32%). mp 83-84 °C; $[\alpha]_D^{22}$ = -3.0 (*c* 2.0, CH_2Cl_2); IR (film / cm^{-1}) ν = 3135 cm^{-1} (OH); ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 5.16 (2H, br s, N*H*O*H*), 3.00 (1H, sex, *J* = 6.2 Hz, C*H*NH), 1.24-1.34 (8H, m, CH_2), 1.11 (3H, d, *J* = 6.4 Hz, CHCH_3), 0.89 (3H, t, *J* = 7.0 Hz, CH_2CH_3); ^{13}C NMR (75 MHz; $CDCl_3$): δ_C = 57.4, 33.4, 32.0, 25.6, 22.6, 17.5, 14.1; HRMS (ES): *m/z* calculated for $C_7H_{18}NO$ [M + H]$^+$: 132.1388; found: 132.1397.



(E)-4-methoxybenzaldehyde oxime 137

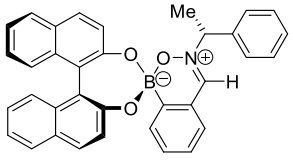
Hydroxylamine hydrochloride (104 mg, 1.50 mmol) was dissolved in 5:1 ethanol:water (10 mL) and cooled to 0 °C. *p*-Anisaldehyde (0.09 mL, 0.75 mmol) was added to the resultant solution followed by the addition of sodium acetate (184 mg, 2.25 mmol) portionwise. The reaction was warmed to room temperature and stirred for a further 24 hours. The ethanol was removed under reduced pressure and the reaction mixture diluted with water followed by extraction with dichloromethane (3 x 10 mL). The combined organic layers were washed with dilute NaOH (10 mL), dried over magnesium sulphate and the solvent removed under reduced pressure to afford the title compound as a white solid (107 mg, 94%). mp 59-61 °C;[214] IR (film / cm^{-1}) ν = 3168 cm^{-1} (OH), 1606 cm^{-1} (C=N); ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 8.40 (1H, br, s, O*H*), 8.11 (1H, s, NC*H*), 7.52 (2H, d, *J* = 8.8 Hz, Ar*H*), 6.91 (2H, d, *J* = 8.8 Hz, Ar*H*), 3.83 (3H, s, CH_3O); ^{13}C NMR (75 MHz; $CDCl_3$): δ_C = 161.1,

133.0, 128.5, 124.6, 114.3, 55.3; HRMS (ES): *m/z* calculated for $C_8H_{10}NO_2$ [M + H]$^+$: 152.0711; found: 152.0690.



(11b'R)-3-((R)-1-phenylethyl)spiro[benzo[d][1,2,6]oxazaborinine-1,4'-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaborepin]-3-ium-1-uide 138a

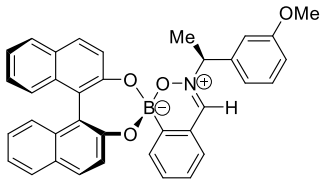
The title compound was prepared according to General Procedure 5 using (*R*)-*N*-(1-phenylethyl)hydroxylamine (**135a**, 30 mg, 0.22 mmol), (*R*)-BINOL (69 mg, 0.24 mmol), 2-formylphenylboronic acid (33 mg, 0.22 mmol) and Cs_2CO_3 (78 mg, 0.24 mmol) to afford diastereomer (*R*,*R*)-**138a**. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H(*R*,*R*) = 8.11 (1H, s, *H*CN), 7.98-7.91 (3H, m, Ar*H*), 7.83 (1H, d, *J* = 8.7 Hz, Ar*H*), 7.50-7.45 (3H, m, Ar*H*), 7.41-7.36 (4H, m, Ar*H*), 7.31 (1H, d, *J* = 8.7 Hz, Ar*H*), 7.29-7.15 (8H, m, Ar*H*), 7.07 (1H, d, *J* = 8.6 Hz, Ar*H*), 5.08 (1H, q, *J* = 7.0 Hz, CH_3CH), 1.69 (3H, d, *J* = 7.0 Hz, CH_3); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B(*R*,*R*) = 12.0; ^{13}C NMR (75 MHz; $CDCl_3$): δ_C(*R*,*R*) = 154.7, 154.3, 152.6, 143.9, 135.8, 135.5, 133.5, 133.4, 131.5, 130.1, 130.0, 129.6, 129.2, 128.9, 128.3, 128.1, 127.7, 127.3, 127.2, 127.1, 126.2, 125.3, 125.2, 124.7, 123.9, 123.7, 123.3, 122.7, 122.6, 117.9, 112.5, 71.6, 19.2.



(11b'S)-3-((R)-1-phenylethyl)spiro[benzo[d][1,2,6]oxazaborinine-1,4'-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaborepin]-3-ium-1-uide 139a

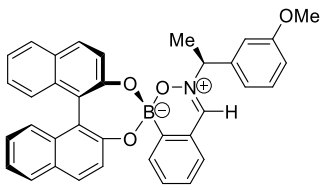
The title compound was prepared according to General Procedure 5 using (*R*)-*N*-(1-phenylethyl)hydroxylamine (**135a**, 30 mg, 0.22 mmol), (*S*)-BINOL (69 mg, 0.24 mmol), 2-formylphenylboronic acid (33 mg, 0.22 mmol) and Cs_2CO_3 (78 mg, 0.24 mmol) to afford diastereoisomer (*R*,*S*)-**139a**. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H(*R*,*S*) =

7.93 (1H, s, *H*CN), 7.98-7.91 (3H, m, Ar*H*), 7.83 (1H, d, *J* = 8.7 Hz, Ar*H*), 7.50-7.45 (3H, m, Ar*H*), 7.41-7.36 (4H, m, Ar*H*), 7.31 (1H, d, *J* = 8.7 Hz, Ar*H*), 7.29-7.15 (8H, m, Ar*H*), 7.07 (1H, d, *J* = 8.6 Hz, Ar*H*), 5.02 (1H, q, *J* = 7.0 Hz, CH_3CH), 1.67 (3H, d, *J* = 7.0 Hz, CH_3); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B(*R*,*S*) = 12.0; ^{13}C NMR (75 MHz; $CDCl_3$): δ_C(*R*,*S*) = 154.5, 152.7, 143.8, 135.7, 135.4, 134.8, 133.7, 133.3, 131.6, 130.7, 130.0, 129.8, 129.5, 129.3, 128.7, 128.5, 128.0, 127.8, 127.3, 127.0, 126.2, 126.0, 125.1, 124.6, 123.8, 123.6, 123.2, 122.8, 122.5, 117.9, 112.3, 71.8, 18.5.



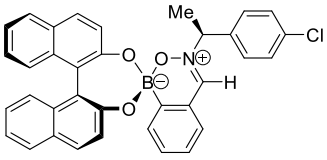
(11b'S)-3-((S)-1-(3-methoxyphenyl)ethyl)spiro[benzo[d][1,2,6]oxazaborinine-1,4'-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaborepin]-3-ium-1-uide 138b

The title compound was prepared according to General Procedure 5 using (*S*)-*N*-(1-(3-methoxyphenyl)ethyl)hydroxylamine (**135b**, 30 mg, 0.18 mmol), (*S*)-BINOL (57 mg, 0.20 mmol), 2-formylphenylboronic acid (27 mg, 0.18 mmol) and Cs_2CO_3 (64 mg, 0.20 mmol) to afford diastereoisomer (*S*,*S*)-**138b**. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H(*S*,*S*) = 8.23 (1H, s, *H*CN), 7.92-7.89 (2H, m, Ar*H*), 7.87-7.83 (1H, m, Ar*H*), 7.67 (1H, d, *J* = 8.8 Hz, Ar*H*), 7.47-7.40 (3H, m, Ar*H*), 7.37-7.33 (3H, m, Ar*H*), 7.31-7.28 (3H, m, Ar*H*), 7.25-7.18 (4H, m, Ar*H*), 7.08 (1H, d, *J* = 8.7 Hz, Ar*H*), 7.05-7.02 (1H, m, Ar*H*), 6.80 (1H, d, *J* = 7.6 Hz, Ar*H*), 5.15 (1H, q, *J* = 7.0, CH_3CH), 3.44 (3H, s, CH_3O), 1.74 (3H, d, *J* = 6.9 Hz, CH_3); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B(*S*,*S*) = 12.0; ^{13}C NMR (75 MHz; $CDCl_3$): δ_C(*S*,*S*) = 160.1, 154.6, 154.5, 152.7, 144.1, 137.5, 135.5, 133.8, 133.5, 133.3, 131.3, 130.7, 130.5, 130.1, 129.6, 129.2, 128.8, 128.6, 127.7, 127.2, 127.1, 126.1, 125.2, 123.8, 123.6, 123.2, 122.7, 122.6, 119.5, 115.6, 113.0, 112.4, 112.3, 71.7, 55.2, 19.5.



(11b'R)-3-((S)-1-(3-methoxyphenyl)ethyl)spiro[benzo[d][1,2,6]oxazaborinine-1,4'-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaborepin]-3-ium-1-uide 139a

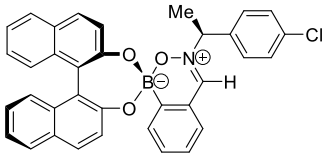
The title compound was prepared according to General Procedure 5 using (*S*)-*N*-(1-(3-methoxyphenyl)ethyl)hydroxylamine (**135b**, 30 mg, 0.18 mmol), (*R*)-BINOL (57 mg, 0.20 mmol), 2-formylphenylboronic acid (27 mg, 0.18 mmol) and Cs_2CO_3 (64 mg, 0.20 mmol) to afford diastereoisomer (*S*,*R*)-**139b**. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H(*S*,*R*) = 7.93 (1H, s, *H*CN), 7.92-7.89 (2H, m, Ar*H*), 7.87-7.83 (1H, m, Ar*H*), 7.79 (1H, d, *J* = 8.8 Hz, Ar*H*), 7.47-7.40 (3H, m, Ar*H*), 7.37-7.33 (3H, m, Ar*H*), 7.31-7.28 (3H, m, Ar*H*), 7.25-7.18 (4H, m, Ar*H*), 7.08 (1H, d, *J* = 8.7 Hz, Ar*H*), 7.05-7.02 (1H, m, Ar*H*), 6.98 (1H, d, *J* = 7.6 Hz, Ar*H*), 5.09 (1H, q, *J* = 7.0 Hz, CH_3C*H*), 3.74 (3H, s, CH_3O), 1.89 (3H, d, *J* = 6.9, C*H*$_3$); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B(*S*,*R*) = 12.0; ^{13}C NMR (75 MHz; $CDCl_3$): δ_C(*S*,*R*) = 160.2, 154.4, 154.2, 152.7, 144.0, 136.2, 135.4, 133.5, 133.3, 131.6, 130.6, 130.0, 129.5, 129.1, 128.7, 128.3, 128.0, 127.7, 127.3, 127.0, 126.0, 125.2, 125.1, 124.6, 123.9, 123.7, 123.3, 122.8, 122.4, 120.7, 118.0, 115.5, 114.1, 71.6, 55.4, 18.4.



(11b'S)-3-((S)-1-(4-chlorophenyl)ethyl)spiro[benzo[d][1,2,6]oxazaborinine-1,4'-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaborepin]-3-ium-1-uide 138c

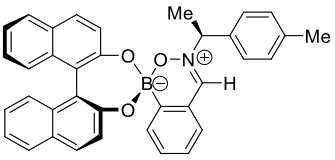
The title compound was prepared according to General Procedure 5 using (*S*)-*N*-(1-(4-chlorophenyl)ethyl)hydroxylamine (**135c**, 30 mg, 0.17 mmol), (*S*)-BINOL (55 mg, 0.19 mmol), 2-formylphenylboronic acid (26 mg, 0.17 mmol) and Cs_2CO_3 (63 mg, 0.19 mmol) to afford diastereoisomer (*S*,*S*)-**138c**. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H(*S*,*S*) = 8.22 (1H, s, *H*CN), 7.95 (2H, d, *J* = 8.2 Hz, Ar*H*), 7.84 (1H, d, *J* = 8.8 Hz,

Ar*H*), 7.78 (1H, d, *J* = 8.7 Hz, Ar*H*), 7.44-7.35 (5H, m, Ar*H*), 7.30-7.27 (1H, m, Ar*H*), 7.24-7.18 (6H, m, Ar*H*), 7.11 (2H, m, Ar*H*), 7.03 (1H, d, *J* = 7.7 Hz, Ar*H*), 6.95 (1H, d, *J* = 8.7 Hz, Ar*H*), 5.02 (1H, q, *J* = 7.0 Hz, CH_3CH), 1.57 (3H, d, *J* = 7.0 Hz, CH_3); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B(*S*,*S*) = 11.7; ^{13}C NMR (75 MHz; $CDCl_3$): δ_C(*S*,*S*) = 154.5, 154.1, 152.7, 144.0, 135.9, 135.6, 135.5, 133.8, 133.2, 131.4, 130.6, 129.9, 129.3, 129.1, 128.8, 128.6, 128.0, 127.8, 127.1, 127.0, 126.0, 125.3, 125.2, 124.6, 123.7, 123.6, 123.5, 123.3, 122.7, 122.5, 117.9, 70.8, 19.3.



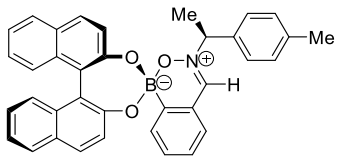
(11b'R)-3-((S)-1-(4-chlorophenyl)ethyl)spiro[benzo[d][1,2,6]oxazaborinine-1,4'-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaborepin]-3-ium-1-uide 139c

The title compound was prepared according to General Procedure 5 using (*S*)-*N*-(1-(4-chlorophenyl)ethyl)hydroxylamine (**135c**, 30 mg, 0.17 mmol), (*R*)-BINOL (55 mg, 0.19 mmol), 2-formylphenylboronic acid (26 mg, 0.17 mmol) and Cs_2CO_3 (63 mg, 0.19 mmol) to afford diastereoisomer (*S*,*R*)-**139c**. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H(*S*,*R*) = 8.01 (1H, s, *H*CN), 7.95 (2H, d, *J* = 8.2 Hz, Ar*H*), 7.89 (1H, d, *J* = 8.8 Hz, Ar*H*), 7.77 (1H, d, *J* = 8.7 Hz, Ar*H*), 7.44-7.35 (5H, m, Ar*H*), 7.30-7.27 (1H, m, Ar*H*), 7.24-7.18 (6H, m, Ar*H*), 7.11 (2H, m, Ar*H*), 7.03 (1H, d, *J* = 7.7 Hz, Ar*H*), 6.83 (1H, d, *J* = 8.7 Hz, Ar*H*), 4.94 (1H, q, *J* = 7.0 Hz, CH_3CH), 1.58 (3H, d, *J* = 7.0 Hz, CH_3); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B(*S*,*R*) = 11.7; ^{13}C NMR (75 MHz; $CDCl_3$): δ_C(*S*,*R*) = 154.4, 154.0, 152.6, 143.9, 136.1, 135.7, 133.4, 133.3, 131.7, 130.0, 129.6, 129.4, 128.7, 128.5, 128.3, 127.9, 127.8, 127.3, 127.2, 125.9, 125.1, 125.0, 124.5, 123.8, 123.4, 123.2, 123.1, 122.6, 122.3, 119.1, 117.9, 71.2, 18.7.



(11b'S)-3-((S)-1-(p-tolyl)ethyl)spiro[benzo[d][1,2,6]oxazaborinine-1,4'-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaborepin]-3-ium-1-uide 138d

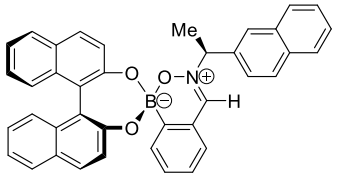
The title compound was prepared according to General Procedure 5 using (*S*)-*N*-(1-(*p*-tolyl)ethyl)hydroxylamine (**135d**, 30 mg, 0.20 mmol), (*S*)-BINOL (62 mg, 0.22 mmol), 2-formylphenylboronic acid (30 mg, 0.20 mmol) and Cs_2CO_3 (71 mg, 0.22 mmol) to afford diastereoisomer (*S*,*S*)-**138d** which was recrystallized from $CDCl_3$ for X-ray crystallographic analysis. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H(*S*,*S*) = 8.06 (1H, s, *H*CN), 7.96 (2H, dd, J_1 = 7.9 Hz, J_2 = 3.7 Hz, Ar*H*), 7.90 (1H, d, *J* = 8.6 Hz, Ar*H*), 7.70 (1H, d, *J* = 8.7 Hz, Ar*H*), 7.49 (2H, t, *J* = 8.7 Hz, Ar*H*), 7.45 (1H, t, *J* = 7.5 Hz, Ar*H*), 7.42-7.39 (2H, m, Ar*H*), 7.31 (1H, d, *J* = 7.4 Hz, Ar*H*), 7.29-7.19 (8H, m, Ar*H*), 7.17-7.14 (2H, m, Ar*H*), 7.11 (1H, d, *J* = 7.7 Hz, Ar*H*), 5.15 (1H, q, *J* = 6.9 Hz, CH_3C*H*), 2.40 (3H, s, ArCH_3), 1.73 (3H, d, *J* = 6.9 Hz, CH_3); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B(*S*,*S*) = 12.0; ^{13}C NMR (75 MHz; $CDCl_3$): δ_C(*S*,*S*) = 154.7, 154.3, 152.7, 143.6, 140.2, 140.0, 135.5, 133.7, 133.4, 132.4, 131.7, 131.5, 130.8, 130.2, 130.0, 129.9, 128.6, 128.3, 127.9, 127.3, 126.2, 125.1, 125.0, 124.5, 123.9, 123.8, 123.7, 123.1, 122.7, 122.6, 117.9, 71.5, 21.3, 19.1.



(11b'R)-3-((S)-1-(p-tolyl)ethyl)spiro[benzo[d][1,2,6]oxazaborinine-1,4'-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaborepin]-3-ium-1-uide 139d

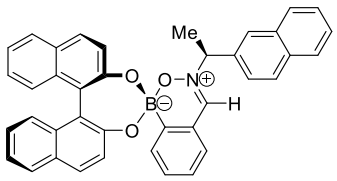
The title compound was prepared according to General Procedure 5 using (*S*)-*N*-(1-(*p*-tolyl)ethyl)hydroxylamine (**135d**, 30 mg, 0.20 mmol), (*R*)-BINOL (62 mg, 0.22 mmol), 2-formylphenylboronic acid (30 mg, 0.20 mmol) and Cs_2CO_3 (71 mg, 0.22 mmol) to afford diastereoisomer (*S*,*R*)-**139d**. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H(*S*,*R*) = 7.96 (2H, dd, J_1 = 7.9 Hz, J_2 = 3.7 Hz, Ar*H*), 7.90 (1H, s, *H*CN), 7.90 (1H, d, *J* = 8.6 Hz, Ar*H*), 7.84 (1H, d, *J* = 8.7 Hz, Ar*H*), 7.49 (2H, t, *J* = 8.7 Hz, Ar*H*), 7.45 (1H, t, *J* = 7.5 Hz, Ar*H*), 7.42-7.39 (2H, m, Ar*H*), 7.32 (1H, d, *J* = 7.4 Hz, Ar*H*), 7.29-7.19 (8H, m, Ar*H*), 7.17-7.14 (2H, m, Ar*H*), 7.11 (1H, d, *J* = 7.7 Hz, Ar*H*), 5.10 (1H, q, *J* = 6.9 Hz, CH_3C*H*), 2.46 (3H, s, ArCH_3), 1.80 (3H, d, *J* = 6.9 Hz, CH_3); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B(*S*,*R*) = 12.0; ^{13}C NMR (75 MHz; $CDCl_3$): δ_C(*S*,*R*) = 154.3, 143.7, 140.1, 135.3, 133.8, 133.5, 133.4, 131.8, 131.6, 130.6,

130.1, 130.0, 129.4, 129.2, 128.7, 128.5, 128.0, 127.7, 127.3, 127.1, 126.1, 125.2, 125.1, 124.6, 123.9, 123.8, 123.6, 123.2, 122.9, 122.4, 117.9, 71.6, 21.4, 18.5.



(11b'S)-3-((S)-1-(naphthalen-2-yl)ethyl)spiro[benzo[d][1,2,6]oxazaborinine-1,4'-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaborepin]-3-ium-1-uide 138e

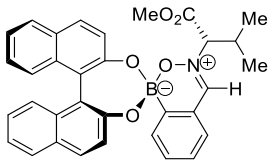
The title compound was prepared according to General Procedure 5 using (*S*)-*N*-(1-(naphthalen-2-yl)ethyl)hydroxylamine (**135e**, 30 mg, 0.16 mmol), (*S*)-BINOL (50 mg, 0.18 mmol), 2-formylphenylboronic acid (24 mg, 0.16 mmol) and Cs_2CO_3 (57 mg, 0.18 mmol) to afford diastereoisomer (*S*,*S*)-**138e**. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H(*S*,*S*) = 8.21 (1H, s, *H*CN), 7.90 (2H, t, *J* = 9.1 Hz, Ar*H*), 7.84-7.73 (5H, m, Ar*H*), 7.64-7.56 (2H, m, Ar*H*), 7.44-7.36 (4H, m, Ar*H*), 7.34-7.28 (3H, m, Ar*H*), 7.27-7.20 (3H, m, Ar*H*), 7.19-7.12 (3H, m, Ar*H*), 6.84 (1H, d, *J* = 8.7 Hz, Ar*H*), 5.34 (1H, q, *J* = 7.0 Hz, CH_3C*H*), 1.83 (3H, d, *J* = 6.9 Hz, CH_3); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B(*S*,*S*) = 11.7; ^{13}C NMR (75 MHz; $CDCl_3$): δ_C(*S*,*S*) = 154.7, 154.5, 143.8, 135.6, 133.8, 133.7, 133.5, 132.9, 131.8, 131.5, 130.9, 130.0, 129.9, 129.4, 128.4, 128.3, 128.2, 127.9, 127.3, 127.2, 127.0, 126.2, 125.4, 125.1, 125.0, 124.5, 124.2, 123.8, 123.5, 123.4, 123.2, 123.1, 122.7, 122.6, 122.4, 122.3, 117.9, 71.7, 19.3.



(11b'R)-3-((S)-1-(naphthalen-2-yl)ethyl)spiro[benzo[d][1,2,6]oxazaborinine-1,4'-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaborepin]-3-ium-1-uide 139e

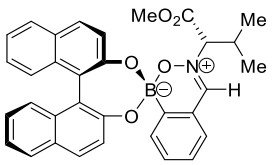
The title compound was prepared according to General Procedure 5 using (*S*)-*N*-(1-(naphthalen-2-yl)ethyl)hydroxylamine (**135e**, 30 mg, 0.16 mmol), (*R*)-BINOL (50 mg, 0.18 mmol), 2-formylphenylboronic acid (24 mg, 0.16 mmol) and Cs_2CO_3 (57

mg, 0.18 mmol) to afford diastereoisomer (*S*,*R*)-**139e**. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H(*S*,*R*) = 7.97 (1H, s, *H*CN), 7.90 (2H, t, *J* = 9.1 Hz, Ar*H*), 7.84-7.73 (5H, m, Ar*H*), 7.64-7.56 (2H, m, Ar*H*), 7.44-7.36 (4H, m, Ar*H*), 7.34-7.28 (3H, m, Ar*H*), 7.27-7.20 (3H, m, Ar*H*), 7.19-7.12 (3H, m, Ar*H*), 6.85 (1H, d, *J* = 8.7 Hz, Ar*H*), 5.31 (1H, q, *J* = 7.0 Hz, CH_3C*H*), 1.93 (3H, d, *J* = 6.9 Hz, CH_3); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B(*S*,*R*) = 11.7; ^{13}C NMR (75 MHz; $CDCl_3$): δ_C(*S*,*R*) = 154.6, 154.1, 152.7, 144.0, 135.5, 133.9, 133.4, 133.3, 133.2, 131.9, 131.7, 131.1, 130.0, 129.9, 129.5, 129.4, 128.7, 128.6, 128.5, 128.4, 127.9, 127.7, 127.5, 127.3, 127.2, 127.1, 126.9, 126.0, 125.5, 125.0, 124.9, 124.4, 123.8, 123.1, 123.0, 122.7, 122.3, 72.0, 18.6.



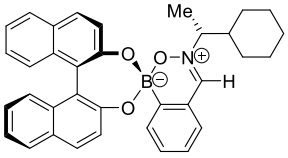
(11b'S)-3-((S)-1-methoxy-3-methyl-1-oxobutan-2-yl)spiro[benzo[d][1,2,6]oxazaborinine-1,4'-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaborepin]-3-ium-1-uide 138f

The title compound was prepared according to General Procedure 5 using (*S*)-methyl 2-(hydroxyamino)-3-methylbutanoate (**135f**, 30 mg, 0.20 mmol), (*S*)-BINOL (64 mg, 0.22 mmol), 2-formylphenylboronic acid (27 mg, 0.20 mmol) and Cs_2CO_3 (64 mg, 0.22 mmol) to afford diastereoisomer (*S*,*S*)-**138f**. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H(*S*,*S*) = 8.50 (1H, s, *H*CN), 7.93-7.83 (4H, m, Ar*H*), 7.51 (1H, t, *J* = 7.3 Hz, Ar*H*), 7.47-7.41 (3H, m, Ar*H*), 7.39-7.29 (5H, m, Ar*H*), 7.26-7.20 (2H, m, Ar*H*), 7.15 (1H, d, *J* = 8.7 Hz, Ar*H*), 4.39 (1H, d, *J* = 9.0 Hz, C*H*CO_2Me), 3.85 (3H, s, CH_3O), 2.53 (1H, hept, *J* = 9.0 Hz, C*H*CH_3), 1.05 (6H, dd, J_1 = 22.6 Hz, J_2 = 6.7 Hz, CH_3); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B(*S*,*S*) = 11.5; ^{13}C NMR (75 MHz; $CDCl_3$): δ_C(*S*,*S*) = 167.4, 154.6, 154.3, 152.7, 147.2, 136.2, 133.7, 133.5, 133.4, 133.3, 131.5, 130.1, 130.0, 128.8, 128.7, 128.4, 128.0, 127.9, 126.1, 124.5, 123.8, 123.7, 123.6, 123.2, 122.5, 122.4, 117.9, 111.9, 78.8, 53.5, 31.5, 19.7, 18.7.



(11b'R)-3-((S)-1-methoxy-3-methyl-1-oxobutan-2-yl)spiro[benzo[d][1,2,6]oxazaborinine-1,4'-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaborepin]-3-ium-1-uide 139f

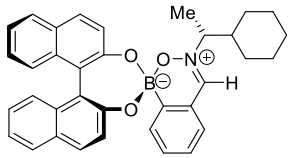
The title compound was prepared according to General Procedure 5 using (*S*)-methyl 2-(hydroxyamino)-3-methylbutanoate (**135f**, 30 mg, 0.20 mmol), (*R*)-BINOL (64 mg, 0.22 mmol), 2-formylphenylboronic acid (27 mg, 0.20 mmol) and Cs_2CO_3 (64 mg, 0.22 mmol) to afford diastereoisomer (*S*,*R*)-**139f**. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H(*S*,*R*) = 8.48 (1H, s, *H*CN), 7.93-7.83 (4H, m, Ar*H*), 7.51 (1H, t, *J* = 7.3 Hz, Ar*H*), 7.47-7.41 (3H, m, Ar*H*), 7.39-7.29 (5H, m, Ar*H*), 7.26-7.20 (2H, m, Ar*H*), 7.11 (1H, d, *J* = 8.7 Hz, Ar*H*), 4.37 (1H, d, *J* = 9.0 Hz, C*H*CO_2Me), 3.77 (3H, s, CH_3O), 2.56 (1H, hept, *J* = 9.0 Hz, C*H*CH_3), 1.11 (6H, dd, J_1 = 38.8 Hz, J_2 = 6.7 Hz, CH_3); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B(*S*,*R*) = 11.5; ^{13}C NMR (75 MHz; $CDCl_3$): δ_C(*S*,*R*) = 167.0, 154.4, 154.2, 152.7, 146.7, 136.0, 133.4, 131.6, 130.9, 130.2, 130.0, 129.3, 128.5, 128.3, 127.9, 127.3, 127.2, 125.8, 125.1, 124.5, 123.9, 123.6, 123.2, 122.7, 122.4, 117.9, 111.9, 78.7, 53.4, 31.2, 19.1, 18.9.



(11b'R)-3-((R)-1-cyclohexylethyl)spiro[benzo[d][1,2,6]oxazaborinine-1,4'-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaborepin]-3-ium-1-uide 138g

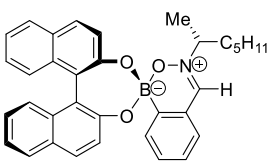
The title compound was prepared according to General Procedure 5 using (*R*)-*N*-(1-cyclohexylethyl)hydroxylamine (**135g**, 30 mg, 0.21 mmol), (*R*)-BINOL (66 mg, 0.23 mmol), 2-formylphenylboronic acid (31 mg, 0.21 mmol) and Cs_2CO_3 (75 mg, 0.23 mmol) to afford diastereoisomer (*S*,*R*)-**138g**. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H(*R*,*R*) = 7.99 (1H, s, *H*CN), 7.94-7.84 (4H, m, Ar*H*), 7.49 (1H, t, *J* = 6.8 Hz, Ar*H*), 7.42 (2H, t, *J* = 8.6 Hz, Ar*H*), 7.38-7.28 (7H, m, Ar*H*), 7.24-7.20 (2H, m,

Ar*H*), 3.68 (1H, quin, *J* = 6.7 Hz, C*H*CH$_3$), 1.94-1.87 (1H, m, C*H*), 1.71-1.59 (4H, m, CH_2), 1.50 (3H, d, *J* = 6.7 Hz, CH_3), 1.22-1.01 (4H, m, CH_2), 0.89-0.82 (2H, m, CH_2); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B(*R*,*R*) = 11.8; ^{13}C NMR (75 MHz; $CDCl_3$): δ_C(*R*,*R*) = 154.8, 154.2, 152.7, 144.0, 135.3, 133.4, 131.7, 130.8, 130.0, 129.2, 128.7, 128.3, 127.9, 127.7, 127.3, 127.1, 125.9, 125.0, 124.6, 124.0, 123.9, 123.7, 123.1, 122.6, 122.5, 117.9, 112.2, 75.0, 39.4, 29.7, 28.5, 25.9, 25.5, 25.3, 16.3.



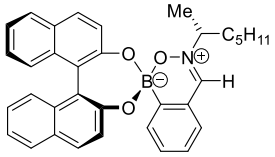
(11b'S)-3-((R)-1-cyclohexylethyl)spiro[benzo[d][1,2,6]oxazaborinine-1,4'-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaborepin]-3-ium-1-uide 139g

The title compound was prepared according to General Procedure 5 using (*R*)-*N*-(1-cyclohexylethyl)hydroxylamine (**135g**, 30 mg, 0.21 mmol), (*S*)-BINOL (66 mg, 0.23 mmol), 2-formylphenylboronic acid (31 mg, 0.21 mmol) and Cs_2CO_3 (75 mg, 0.23 mmol) to afford diastereoisomer (*R*,*S*)-**139g**. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H(*R*,*S*) = 7.90 (1H, s, *H*CN), 7.94-7.84 (4H, m, Ar*H*), 7.49 (1H, t, *J* = 6.8 Hz, Ar*H*), 7.42 (2H, t, *J* = 8.6 Hz, Ar*H*), 7.38-7.28 (7H, m, Ar*H*), 7.24-7.20 (2H, m, Ar*H*), 3.57 (1H, quin, *J* = 6.7 Hz, C*H*CH$_3$), 1.97-1.90 (1H, m, C*H*), 1.71-1.59 (4H, m, CH_2), 1.36 (3H, d, *J* = 6.7 Hz, CH_3), 1.22-1.01 (4H, m, CH_2), 0.84-0.78 (2H, m, CH_2); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B(*R*,*S*) = 11.8; ^{13}C NMR (75 MHz; $CDCl_3$): δ_C(*R*,*S*) = 154.7, 154.4, 152.7, 143.9, 135.2, 133.7, 133.5, 131.6, 130.7, 130.0, 129.1, 128.6, 128.4, 128.0, 127.9, 127.1, 125.8, 125.1, 124.6, 124.0, 123.9, 123.7, 123.2, 122.7, 122.4, 117.9, 112.1, 75.3, 39.6, 29.9, 28.8, 25.8, 25.7, 25.6, 16.2.



(11b'R)-3-((R)-heptan-2-yl)spiro[benzo[d][1,2,6]oxazaborinine-1,4'-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaborepin]-3-ium-1-uide 138h

The title compound was prepared according to General Procedure 5 using (*R*)-*N*-(heptan-2-yl)hydroxylamine (**135h**, 30 mg, 0.23 mmol), (*R*)-BINOL (72 mg, 0.25 mmol), 2-formylphenylboronic acid (34 mg, 0.23 mmol) and Cs_2CO_3 (82 mg, 0.25 mmol) to afford diastereoisomer (*R*,*R*)-**138h**. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H(*R*,*R*) = 8.03 (1H, s, *H*CN), 7.96-7.86 (4H, m, Ar*H*), 7.49-7.44 (3H, m, Ar*H*), 7.41-7.36 (3H, m, Ar*H*), 7.34 (1H, d, *J* = 8.7 Hz, Ar*H*), 7.32-7.22 (5H, m, Ar*H*), 3.89 (1H, sex, *J* = 7.3 Hz, C*H*CH_3), 1.93-1.86 (1H, m, CH_2), 1.54-1.47 (1H, m, CH_2), 1.44 (3H, d, *J* = 7.0 Hz, CHCH_3), 1.24-1.14 (6H, m, CH_2), 0.85 (3H, t, *J* = 7.0 Hz, CH_2CH_3); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B(*R*,*R*) = 11.9; ^{13}C NMR (125 MHz; $CDCl_3$): δ_C(*R*,*R*) = 154.8, 154.3, 152.6, 143.9, 135.2, 133.8, 133.4, 131.5, 130.6, 130.0, 129.2, 128.8, 128.4, 128.1, 127.7, 127.3, 127.1, 126.1, 125.2, 125.1, 124.7, 124.0, 123.8, 123.7, 123.3, 122.5, 117.9, 70.0, 33.7, 31.2, 25.5, 22.5, 18.9, 14.1.



(11b'S)-3-((R)-heptan-2-yl)spiro[benzo[d][1,2,6]oxazaborinine-1,4'-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaborepin]-3-ium-1-uide 139h

The title compound was prepared according to General Procedure 5 using (*R*)-*N*-(heptan-2-yl)hydroxylamine (**135h**, 30 mg, 0.23 mmol), (*S*)-BINOL (72 mg, 0.25 mmol), 2-formylphenylboronic acid (34 mg, 0.23 mmol) and Cs_2CO_3 (82 mg, 0.25 mmol) to afford diastereoisomer (*R*,*S*)-**139h**. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H(*R*,*S*) = 7.99 (1H, s, *H*CN), 7.96-7.86 (3H, m, Ar*H*), 7.79 (1H, d, *J* = 8.6 Hz, Ar*H*), 7.49-7.44 (3H, m, Ar*H*), 7.41-7.36 (3H, m, Ar*H*), 7.32-7.22 (5H, m, Ar*H*), 7.16 (1H, d, *J* = 8.7 Hz, Ar*H*), 3.84 (1H, sex, *J* = 7.3 Hz, C*H*CH_3), 1.93-1.86 (1H, m, CH_2), 1.54-1.47 (1H, m, CH_2), 1.36 (3H, d, *J* = 7.0 Hz, CHCH_3), 1.24-1.14 (6H, m, CH_2), 0.96 (3H, t, *J* = 7.0 Hz, CH_2CH_3); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B(*R*,*S*) = 11.9; ^{13}C NMR (125 MHz; $CDCl_3$): δ_C(*R*,*S*) = 154.6, 154.2, 152.7, 143.6, 135.3, 133.7, 133.5, 131.6, 130.8, 130.0, 129.1, 128.7, 128.4, 128.3, 128.0, 127.9, 127.1, 126.0, 125.1, 124.6, 123.7, 123.6, 123.2, 123.1, 122.7, 122.6, 117.9, 70.3, 33.9, 31.4, 25.8, 22.5, 18.8, 14.0.

5.6 General Procedures for Chapter 4

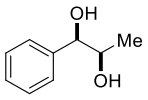
5.6.1 General Procedure 6: Dihydroxylation of Alkenes

Racemic diols **182b,i,j** were prepared according to the literature procedure.[213] AD-mix-α (0.70 g) and AD-mix-β (0.70 g) were dissolved in 1:1 *tert*-butanol:water (10 mL) and stirred at room temperature to produce two clear phases. Methanesulfonamide (1.00 mmol) was added if the alkene is non-terminal and the mixture cooled to 0 °C. The corresponding alkene was then added (1.00 mmol) and the reaction stirred vigorously at 0 °C for 24 hours. Sodium sulfite was added and the reaction allowed to warm to room temperature and stirred for a further one hour. The reaction mixture was extracted with dichloromethane (3 x 10 mL) and when methanesulfonamide was employed the combined organic layers were washed with 2 M potassium hydroxide solution. The combined organic layers were dried over magnesium sulphate and the solvent evaporated under reduced pressure. The crude product was purified by silica gel flash column chromatography (ethyl acetate/hexane) to afford the corresponding dihydroxylated product.

5.6.2 General Procedure 7: Determination of the Enantiomeric Excess of Chiral Diols

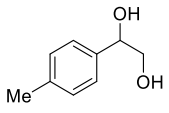
To a solution of 1,3-phenyldiboronic acid (20 mg, 0.12 mmol) suspended in MeOH the appropriate chiral diol (0.24 mmol) and 3Å molecular sieves were added and the suspension stirred for 20 minutes at room temperature, before filtering and evaporating the solvent under reduced pressure. The resultant product was then dissolved in $CDCl_3$ before acquiring a 500 MHz ^1H NMR spectrum.

5.7 Synthesis of Compounds in Chapter 4



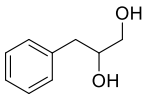
(rac)-1-phenylpropane-1,2-diol 182b

The title compound was prepared according to General Procedure 6 using *trans*-β-methylstyrene (0.13 mL, 1 mmol) and methanesulfonamide (95 mg, 1.00 mmol) to afford diol **182b** as a white solid (128 mg, 84%). mp 54-55 °C;[215] IR (film / cm^{-1}) ν = 3340 cm^{-1} (OH); ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.35-7.25 (5H, m, Ar*H*), 4.36 (1H, app t, PhCH), 3.89-3.83 (1H, m, $CHCH_3$), 2.75 (1H, br s, PhCHOH), 2.62 (1H, br s, CH_3CHOH), 1.06 (3H, app t, CH_3); ^{13}C NMR (75 MHz; $CDCl_3$): δ_C = 141.0, 128.5, 128.2, 126.9, 79.5, 72.3, 18.8; HRMS (ES): m/z calculated for $C_9H_{11}O_2$ $[M - H]^-$: 151.0759; found: 151.0773.



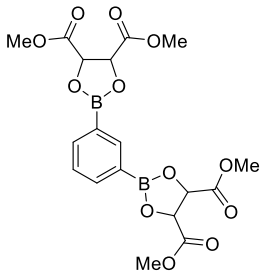
1-(p-tolyl)ethane-1,2-diol 182i

The title compound was prepared according to General Procedure 6 using 4-methylstyrene (0.13 mL, 1.00 mmol) to afford diol **182i** as a white solid (120 mg, 79%). mp 77-78 °C;[216] IR (film / cm^{-1}) ν = 3244 cm^{-1} (OH); ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.25 (2H, d, *J* = 7.4 Hz, Ar*H*), 7.17 (2H, d, *J* = 7.9 Hz, Ar*H*), 4.79 (1H, dd, J_1 = 8.1 Hz, J_2 = 3.7 Hz, C*H*OH), 3.76-3.61 (2H, m, CH_2OH), 2.64 (2H, br s, OH), 2.35 (3H, s, CH_3); ^{13}C NMR (75 MHz; $CDCl_3$): δ_C = 137.8, 137.5, 129.3, 126.0, 74.6, 68.1, 21.2; HRMS (ES): *m/z* calculated for $C_9H_{11}O_2$ $[M - H]^-$: 151.0759; found: 151.0775.



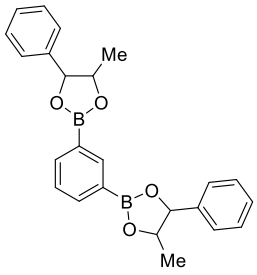
3-phenylpropane-1,2-diol 182j

The title compound was prepared according to General Procedure 6 using allylbenzene (0.13 mL, 1.00 mmol) to afford diol **182j** as an orange oil (94 mg, 62%). ^{1}H NMR (300 MHz; $CDCl_3$): IR (film / cm^{-1}) ν = 3337 cm^{-1} (OH); δ_H = 8.27-8.13 (5H, m, Ar*H*), 3.90-3.82 (1H, m, C*H*OH), 3.61 (1H, dd, J_1 = 11.2 Hz, J_2 = 3.2 Hz, CH_2OH), 3.43 (1H, dd, J_1 = 11.2 Hz, J_2 = 3.2 Hz, CH_2OH), 2.75-2.62 (2H, m, CH_2), 2.23 (2H, br s, O*H*); ^{13}C NMR (75 MHz; $CDCl_3$): δ_C = 137.7, 129.4, 128.7, 126.7, 73.1, 66.1, 39.8; HRMS (ES): *m/z* calculated for $C_9H_{11}O_2$ [M - H]$^-$: 151.0759; found: 151.0775.



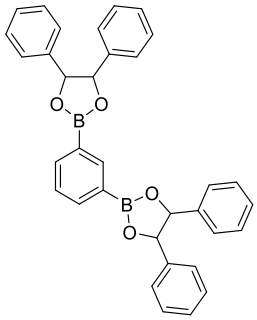
tetramethyl 2,2'-(1,3-phenylene)bis(1,3,2-dioxaborolane-4,5-dicarboxylate) 187/188a

The title compound was prepared according to General Procedure 7 using racemic diol **182a** to afford a Horeau series of diboronate esters as a white solid. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H = 8.59 and 8.57 (1H, app d, Δδ = 0.020 ppm, BCC*H*CB), 8.09 (2H, d, *J* = 7.4 Hz, BAr*H*), 7.51 (1H, t, *J* = 7.5 Hz, BAr*H*), 5.16 (4H, s, C*H*), 3.92 and 3.91 (12H, app d, Δδ = 0.010 ppm, CH_3O); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B = 31.7; ^{13}C NMR (125 MHz; $CDCl_3$): δ_C = 169.8, 142.5 (hetero Ar*C*), 142.4 (homo Ar*C*), 139.0, 127.5, 77.9, 53.1.



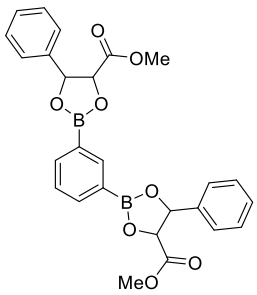
1,3-bis(4-methyl-5-phenyl-1,3,2-dioxaborolan-2-yl)benzene 187/188b

The title compound was prepared according to General Procedure 7 using racemic diol **182b** to afford a Horeau series of diboronate esters as a white solid. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H = 8.51 and 8.50 (1H, app d, $\Delta\delta$ = 0.012 ppm, BCC*H*CB), 8.07 (2H, d, *J* = 7.4 Hz, BAr*H*), 7.49 (1H, t, *J* = 7.5 Hz, BAr*H*), 7.42-7.40 (8H, m, Ar*H*), 7.38-7.35 (2H, m, Ar*H*), 5.07 (2H, d, *J* = 7.5 Hz, C*H*Ph), 4.50 (2H, quin, *J* = 6.2 Hz, C*H*Me), 1.57 (6H, d, *J* = 6.2 Hz, CH_3); ^{11}B NMR (160 MHz; $CDCl_3$): δ_B = 32.6; ^{13}C NMR (125 MHz; $CDCl_3$): δ_C = 142.0 (hetero Ar*C*), 141.9 (homo Ar*C*), 140.6 (hetero Ar*C*), 140.5 (homo Ar*C*), 138.1, 128.7, 128.3, 127.4, 125.7 (hetero Ar*C*), 125.6 (homo Ar*C*), 86.1, 81.7, 21.2.



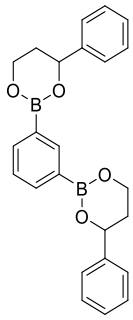
1,3-bis(4,5-diphenyl-1,3,2-dioxaborolan-2-yl)benzene 187/188c

The title compound was prepared according to General Procedure 7 using racemic diol **182c** to afford a Horeau series of diboronate esters as a white solid. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H = 8.65 and 8.63 (1H, app d, $\Delta\delta$ = 0.024 ppm, BCC*H*CB), 8.16 (2H, d, *J* = 7.5 Hz, BAr*H*), 7.53 (1H, t, *J* = 7.3 Hz, BAr*H*), 7.42-7.34 (20H, m, Ar*H*), 5.36 (4H, s, C*H*); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B = 31.5; ^{13}C NMR (125 MHz; $CDCl_3$): δ_C = 141.5, 140.3, 138.6, 128.8, 128.4, 125.9, 125.8, 87.0.



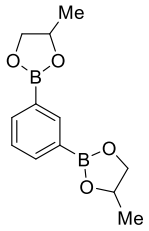
dimethyl 2,2'-(1,3-phenylene)bis(5-phenyl-1,3,2-dioxaborolane-4-carboxylate) 187/188d

The title compound was prepared according to General Procedure 7 using racemic diol **182d** to afford a Horeau series of diboronate esters as a white solid. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H = 8.59 and 8.57 (1H, app d, $\Delta\delta$ = 0.020 ppm, BCC*H*CB), 8.14 (2H, d, *J* = 7.4 Hz, BAr*H*), 7.53 (1H, t, *J* = 7.5 Hz, BAr*H*), 7.47-7.40 (8H, m, Ar*H*), 7.40-7.37 (2H, m, Ar*H*), 5.65 (2H, dd, J_1 = 2.9 Hz, J_2 = 6.1 Hz, C*H*Ph), 4.90 (2H, d, *J* = 6.1 Hz, C*H*CO_2Me), 3.90 (6H, s, CH_3O); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B = 30.7; ^{13}C NMR (125 MHz; $CDCl_3$): δ_C = 171.0, 142.4, 140.3, 138.8, 128.9, 128.6, 127.6, 125.4 (hetero Ar*C*), 125.3 (homo Ar*C*), 82.6, 81.9, 52.8; HRMS (ES): *m/z* calculated for $C_{26}H_{24}B_2O_8Na$ $[M + Na]^+$: 509.1554; found: 509.1540.



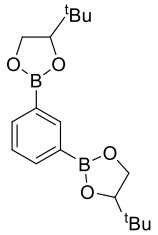
1,3-bis(4-phenyl-1,3,2-dioxaborinan-2-yl)benzene 187/188e

The title compound was prepared according to General Procedure 7 using racemic diol **182e** to afford a Horeau series of diboronate esters as a white solid. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H = 8.47 and 8.46 (1H, app d, $\Delta\delta$ = 0.020 ppm, BCC*H*CB), 8.03 (2H, d, *J* = 7.3 Hz, BAr*H*), 7.47-7.41 (9H, m, Ar*H*), 7.35 (2H, m, Ar*H*), 5.33 (2H, app dd, J_1 = Hz, J_2 = Hz, OC*H*), 4.30-4.17 (4H, m, OCH_2), 2.36 (2H, dq, J_1 = Hz, J_2 = Hz, CH_2), 2.13-2.05 (2H, m, CH_2); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B =; ^{13}C NMR (125 MHz; $CDCl_3$): δ_C = 142.7 (hetero Ar*C*), 142.6 (homo Ar*C*), 139.7 (hetero Ar*C*), 139.6 (homo Ar*C*), 136.4, 128.5, 127.5, 127.0, 125.3, 72.8, 61.0 (hetero Ar*C*), 60.9 (homo Ar*C*), 35.4; HRMS (ES): *m/z* calculated for $C_{24}H_{24}B_2O_4Na$ $[M + Na]^+$: 421.1758; found: 421.1764.



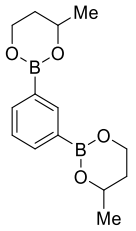
1,3-bis(4-methyl-1,3,2-dioxaborolan-2-yl)benzene 187/188f

The title compound was prepared according to General Procedure 7 using racemic diol **182f** to afford a Horeau series of diboronate esters as a colourless oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H = 8.32 (1H, s, BCC*H*CB), 7.93 (2H, d, *J* = 7.4 Hz, BAr*H*), 7.42 (1H, t, *J* = 7.4 Hz, BAr*H*), 4.74 (2H, sex, *J* = 6.6 Hz, C*H*CH_3), 4.47 (2H, t, *J* = 8.2 Hz, C*H*$_2$O), 3.91 (2H, t, *J* = 8.3 Hz, C*H*$_2$O), 1.43 (6H, d, *J* = 6.2 Hz, C*H*$_3$); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B = 35.7; ^{13}C NMR (125 MHz; $CDCl_3$): δ_C = 141.6, 137.7, 127.3, 73.8, 72.6, 21.8.



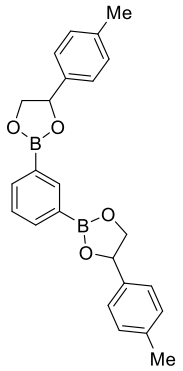
1,3-bis(4-(tert-butyl)-1,3,2-dioxaborolan-2-yl)benzene 187/188g

The title compound was prepared according to General Procedure 7 using racemic diol **182g** to afford a Horeau series of diboronate esters as a colourless oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H = 8.29 (1H, s, BCC*H*CB), 7.93 (2H, d, *J* = 7.4 Hz, BAr*H*), 7.40 (1H, t, *J* = 7.5 Hz, BAr*H*), 4.31-4.25 (4H, m, C*H*$_2$), 4.18-4.11 (2H, m, C*H*), 0.95 (18H, s, C*H*$_3$); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B = 33.8; ^{13}C NMR (125 MHz; $CDCl_3$): δ_C = 141.5, 137.8, 127.2, 85.0, 67.1, 34.0, 24.6.



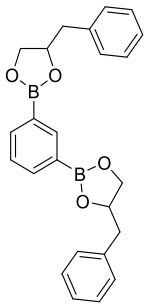
1,3-bis(4-methyl-1,3,2-dioxaborinan-2-yl)benzene 187/188h

The title compound was prepared according to General Procedure 7 using racemic diol **182h** to afford a Horeau series of diboronate esters as a colourless oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H = 8.23 (1H, s, BCC*H*CB), 7.85 (2H, d, *J* = 7.4 Hz, BAr*H*), 7.35 (1H, t, *J* = 7.6 Hz, BAr*H*), 4.34-4.28 (2H, m, C*H*CH_3), 4.23-4.29 (2H, m, CH_2O), 4.16-4.10 (2H, m, CH_2O), 2.03 (2H, dq, J_1 = 14.4 Hz, J_2 = 3.5 Hz, CH_2), 1.84-1.77 (2H, m, CH_2), 1.39 (6H, d, *J* = 6.3 Hz, CH_3); ^{11}B NMR (160 MHz; $CDCl_3$): δ_B = 31.3; ^{13}C NMR (125 MHz; $CDCl_3$): δ_C = 139.2, 135.9, 126.8, 67.6, 61.2, 34.3, 23.0.



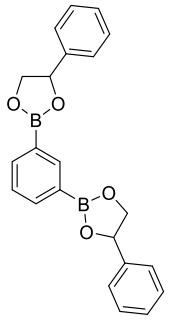
1,3-bis(4-(p-tolyl)-1,3,2-dioxaborolan-2-yl)benzene 187/188i

The title compound was prepared according to General Procedure 7 using racemic diol **182i** to afford a Horeau series of diboronate esters as a white solid. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H = 8.49 (1H, br s, BCC*H*CB), 8.05 (2H, d, *J* = 7.5 Hz, BAr*H*), 7.49 (1H, t, *J* = 7.9 Hz, BAr*H*), 7.30 (4H, d, *J* = 8.5 Hz, Ar*H*), 7.22 (4H, d, *J* = 8.5 Hz, Ar*H*), 5.59 (2H, t, *J* = 7.5 Hz, OC*H*), 4.75 (2H, t, *J* = 8.0 Hz, OCH_2), 4.75 (2H, app t, OCH_2), 2.38 (6H, s, CH_3O); ^{11}B NMR (160 MHz; $CDCl_3$): δ_B = 31.4; ^{13}C NMR (125 MHz; $CDCl_3$): δ_C = 142.0, 138.2, 138.0, 129.5, 127.5, 125.8, 125.7, 79.0, 73.5, 21.2.



1,3-bis(4-benzyl-1,3,2-dioxaborolan-2-yl)benzene 187/188j

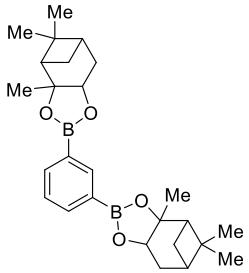
The title compound was prepared according to General Procedure 7 using racemic diol **182j** to afford a Horeau series of diboronate esters as a white solid. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H = 8.32 (1H, s, BCC*H*CB), 7.94 (2H, d, *J* = 7.4 Hz, BAr*H*), 7.42 (1H, t, *J* = 7.4 Hz, BAr*H*), 7.35-7.32 (4H, m, Ar*H*), 7.29-7.25 (6H, m, Ar*H*), 4.84 (2H, quin, *J* = 6.7 Hz, OC*H*), 4.37 (2H, app t, CH_2O), 4.09 (2H, dd, J_1 = 6.9 Hz, J_2 = 8.3 Hz, CH_2O), 3.16 (2H, dd, J_1 = 13.9 Hz, J_2 = 6.2 Hz, CH_2), 2.91 (2H, dd, J_1 = 13.9 Hz, J_2 = 6.9 Hz, CH_2); ^{11}B NMR (160 MHz; $CDCl_3$): δ_B = 31.8; ^{13}C NMR (125 MHz; $CDCl_3$): δ_C = 141.6, 137.9, 136.7 (hetero Ar*C*), 136.6 (homo Ar*C*), 129.4, 128.6, 127.3, 126.8, 77.9, 70.5, 42.2.



1,3-bis(4-phenyl-1,3,2-dioxaborolan-2-yl)benzene 187/188k

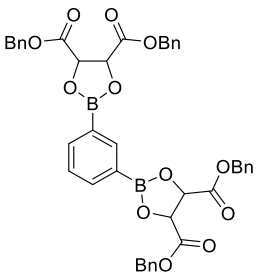
The title compound was prepared according to General Procedure 7 using racemic diol **182k** to afford a Horeau series of diboronate esters as a colourless oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H = 8.48 (1H, br s, BCC*H*CB), 8.06 (2H, d, *J* = 7.4 Hz, BAr*H*), 7.49 (1H, t, *J* = 7.5 Hz, BAr*H*), 7.42-7.39 (8H, m, Ar*H*), 7.37-7.34 (2H, m, Ar*H*), 5.63 (2H, t, *J* = 7.9 Hz, C*H*), 4.77 (2H, t, *J* = 8.5 Hz, CH_2), 5.63 (2H, dd, J_1 = 7.7

Hz, J_2 = 9.0 Hz, CH_2); ^{11}B NMR (160 MHz; $CDCl_3$): δ_B = 32.0; ^{13}C NMR (125 MHz; $CDCl_3$): δ_C = 142.0, 141.1, 138.2, 128.8, 128.2, 127.5, 125.6, 78.9, 73.4.



1,3-bis(3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)benzene 187/188l

The title compound was prepared according to General Procedure 7 using racemic diol **182l** to afford a Horeau series of diboronate esters as a colourless oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H = 8.29 (1H, br s, BCC*H*CB), 7.90 (2H, d, *J* = 7.5 Hz, BAr*H*), 7.38 (1H, t, *J* = 7.4 Hz, BAr*H*), 4.44 (2H, d, *J* = 8.7 Hz, CH_2O), 2.43-2.38 (2H, m, OCHCH_2C*H*), 2.24-2.19 (2H, m, OCC*H*), 2.16-2.13 (2H, m, CH_2), 1.99-1.92 (4H, m, CH_2), 1.47 (6H, s, CH_3CO), 1.30 (6H, s, CH_3), 1.19 (2H, d, *J* = 10.9 Hz, CH_2), 0.88 (6H, s, CH_3); HRMS (ES): *m/z* calculated for $C_{26}H_{26}B_2O_4Na$ $[M + Na]^+$: 457.2697; found: 457.2695.

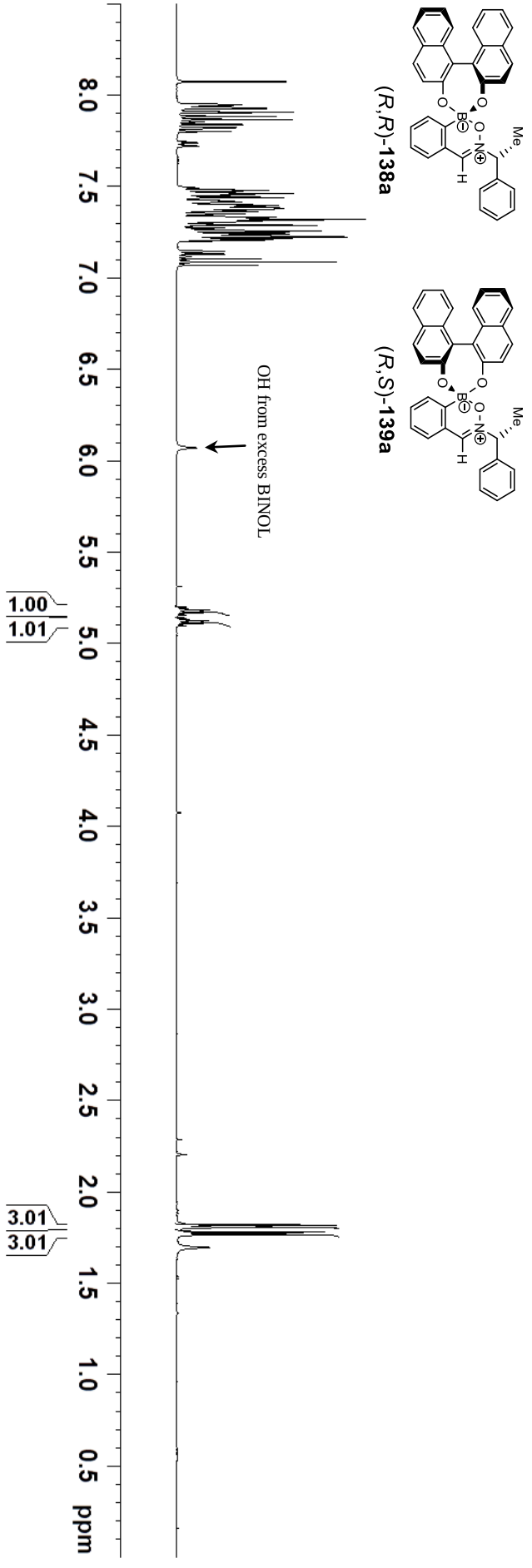


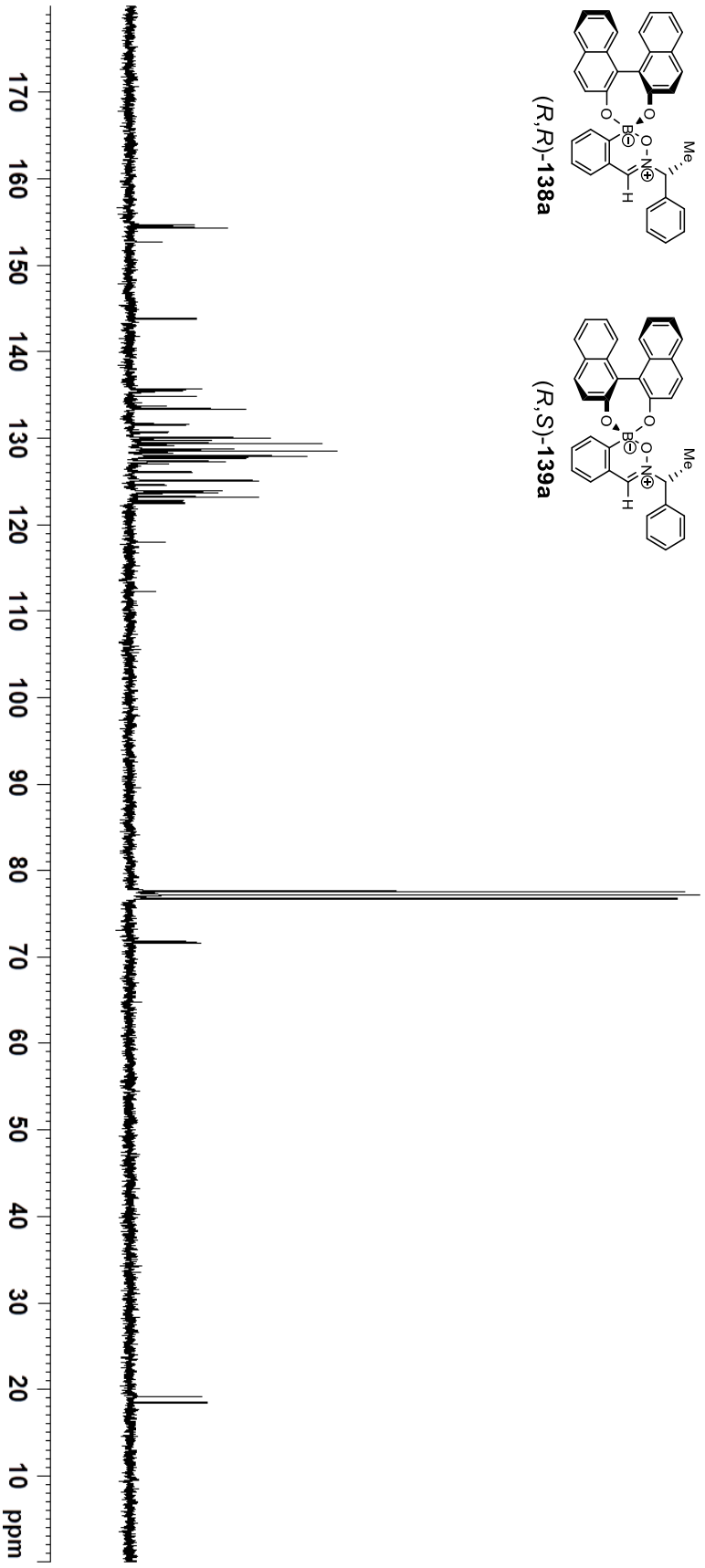
tetrabenzyl 2,2'-(1,3-phenylene)bis(1,3,2-dioxaborolane-4,5-dicarboxylate) 187/188m

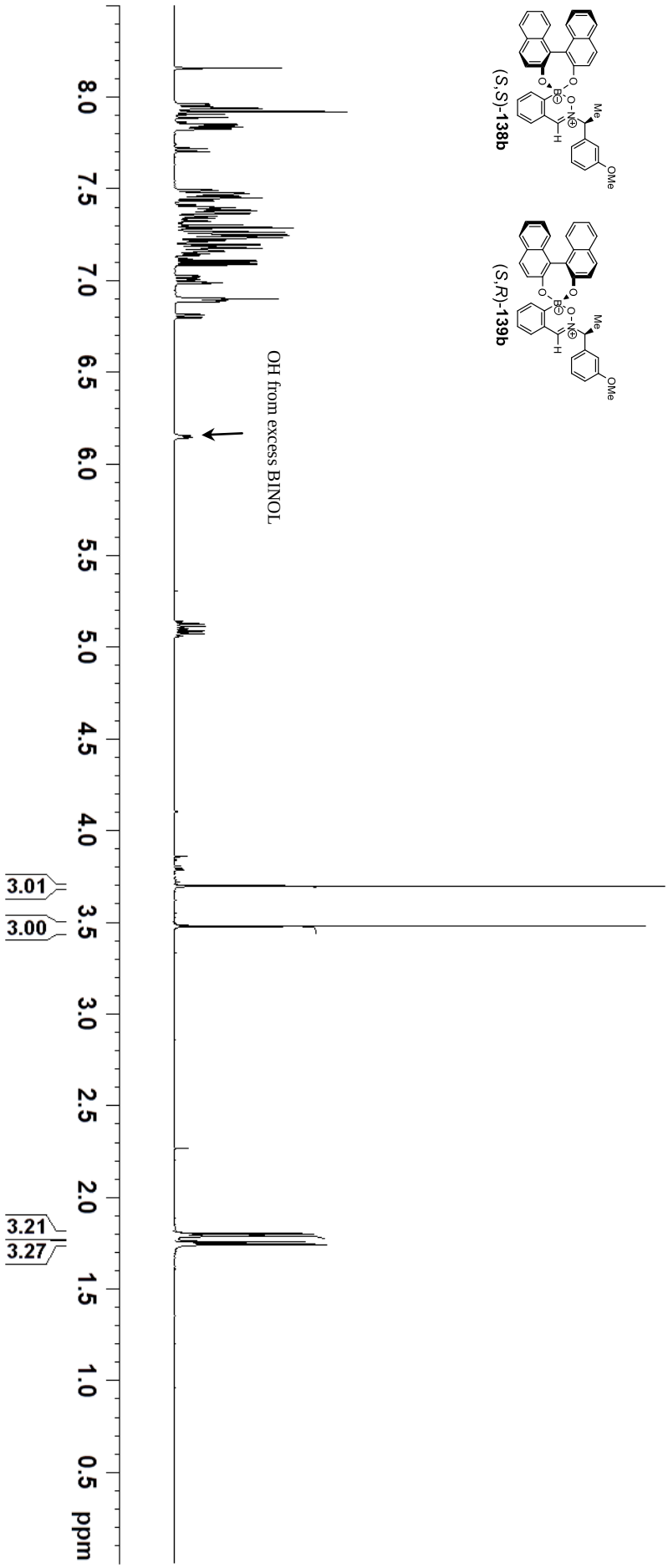
The title compound was prepared according to General Procedure 7 using racemic diol **182m** to afford a Horeau series of diboronate esters as a white solid. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H = 8.49 (1H, br s, BCC*H*CB), 8.08 (2H, d, *J* = 8.8 Hz, BCC*H*CH), 7.50 (1H, t, *J* = 9.4 Hz, BAr*H*), 7.43-7.39 (20H, m, Ar*H*), 5.32 (8H, m,

C*H*$_2$) 5.15 (4H, s, C*H*); ^{11}B NMR (96 MHz; $CDCl_3$): δ_B = 31.3; ^{13}C NMR (125 MHz; $CDCl_3$): δ_C = 171.4, 169.1, 142.5 (hetero Ar*C*), 142.4 (homo Ar*C*), 139.1, 134.9, 128.7, 128.6, 128.4, 128.3, 78.0, 72.1, 68.1, 67.7.

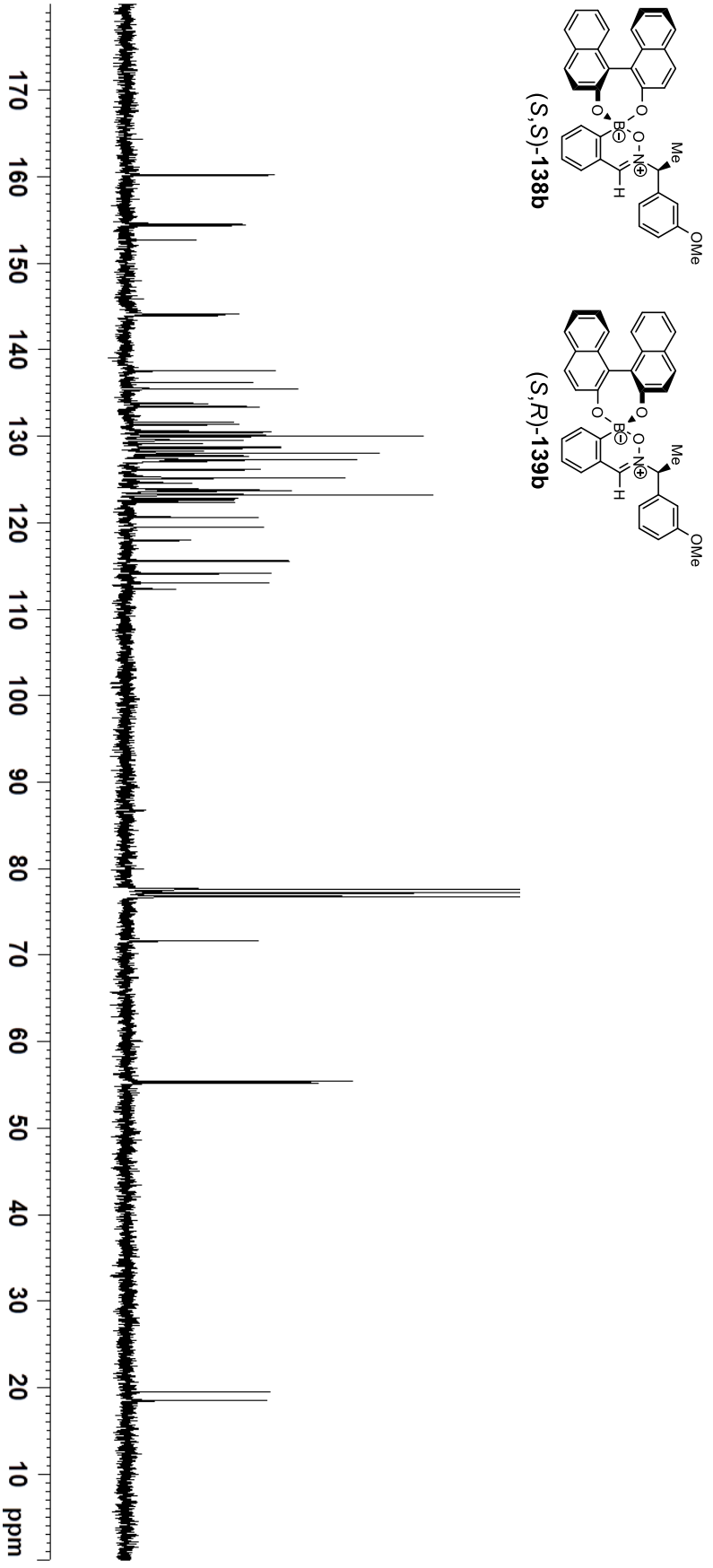
6 Appendix


500 MHz; $CDCl_3$
(*R*,*R*)-**138a**
(*R*,*S*)-**139a**
Me
OH from excess BINOL
1.00
1.01
3.01
3.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

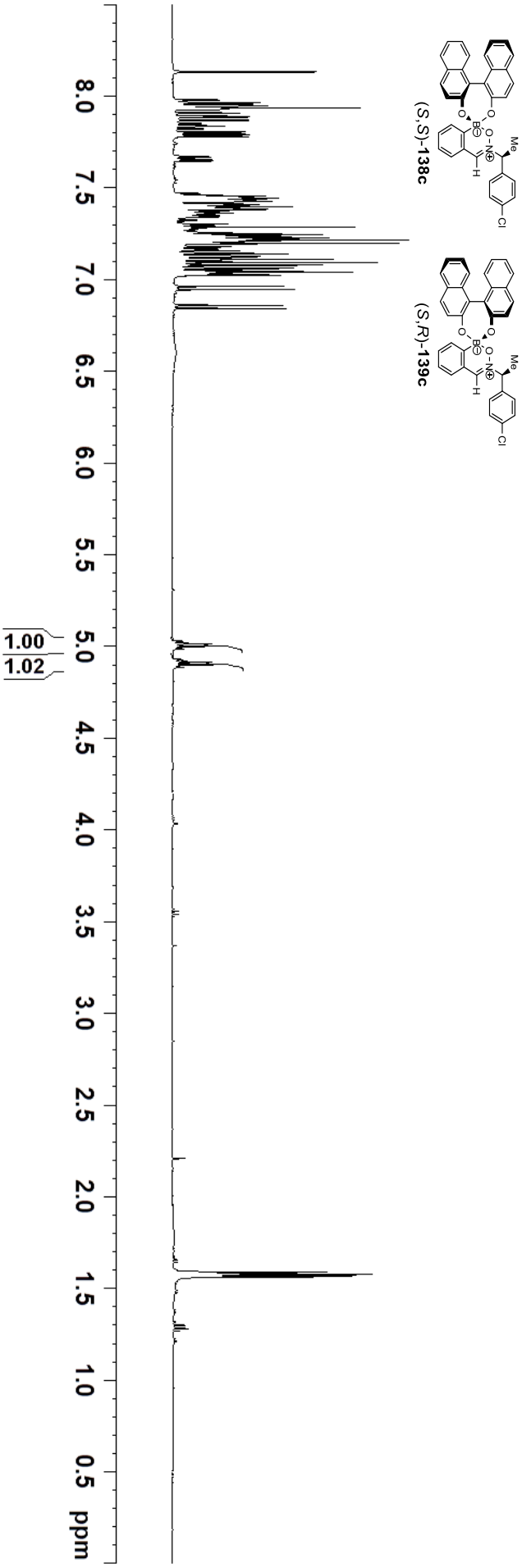

75 MHz; $CDCl_3$
(*R*,*R*)-**138a**
(*R*,*S*)-**139a**
Me
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


500 MHz; $CDCl_3$
(S,S)-**138b**
(S,*R*)-**139b**
OH from excess BINOL
3.01
3.00
3.21
3.27
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

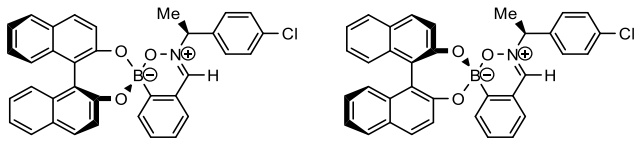
75 MHz; $CDCl_3$


(S,S)-138b
(S,R)-139b
Me
OMe
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

500 MHz; $CDCl_3$

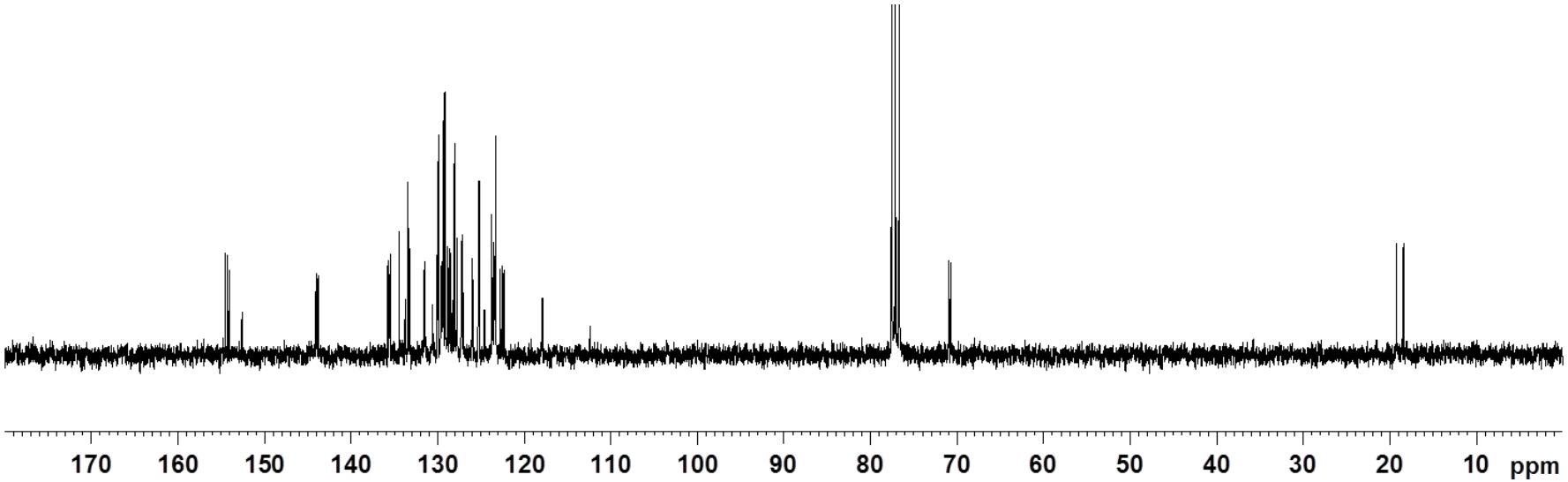


75 MHz; $CDCl_3$

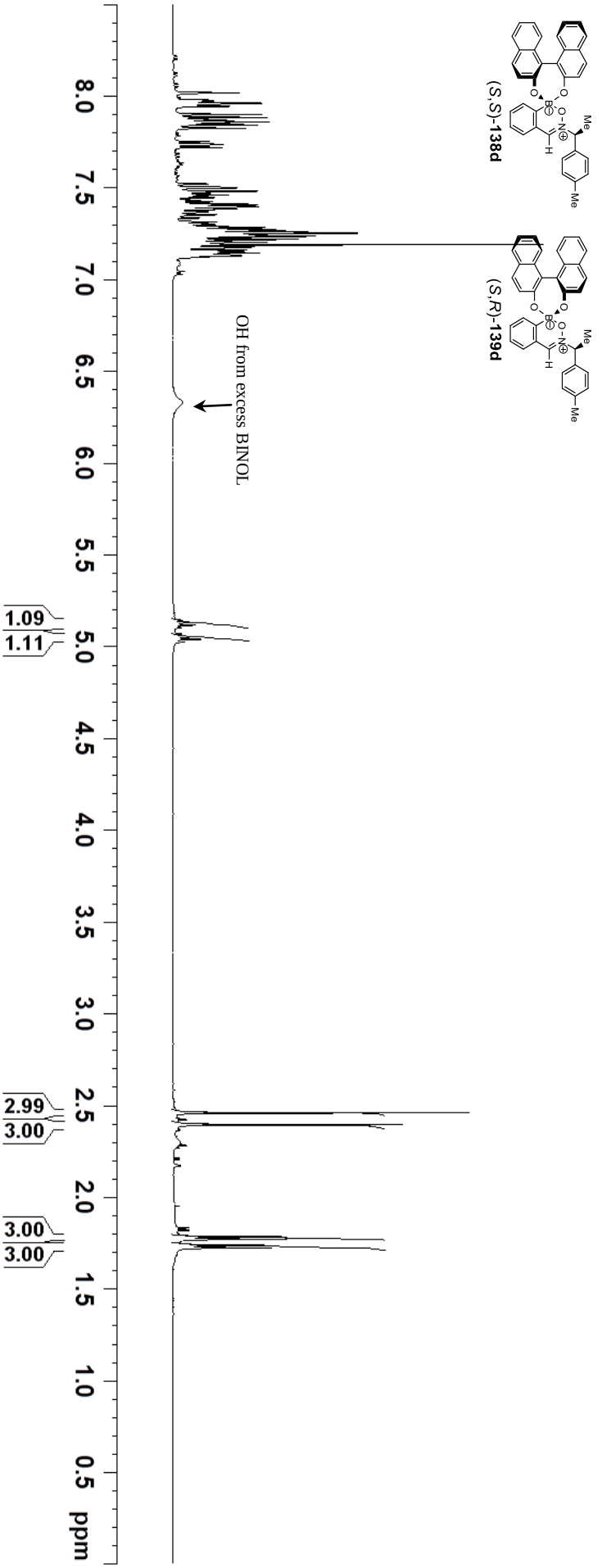


(*S*,*S*)-**138c**

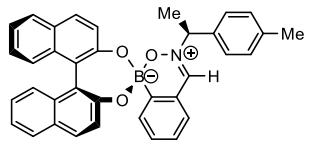
(*S*,*R*)-**139c**



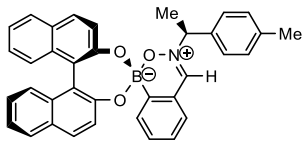
500 MHz; $CDCl_3$



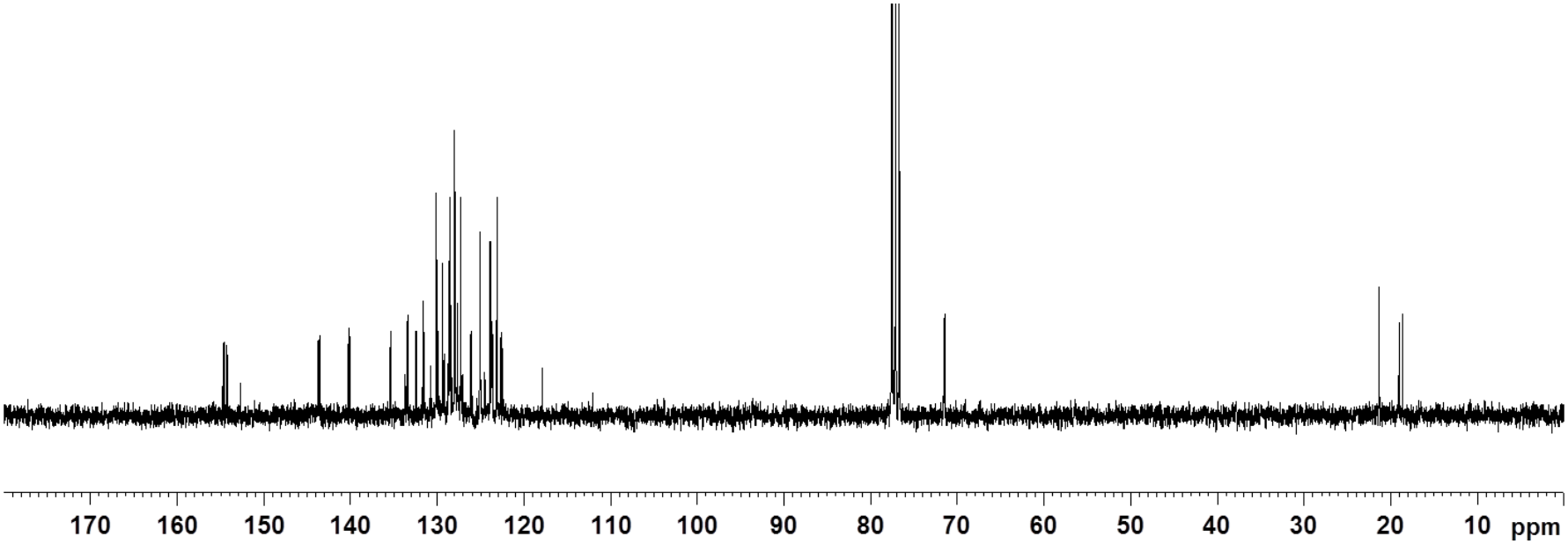
75 MHz; $CDCl_3$



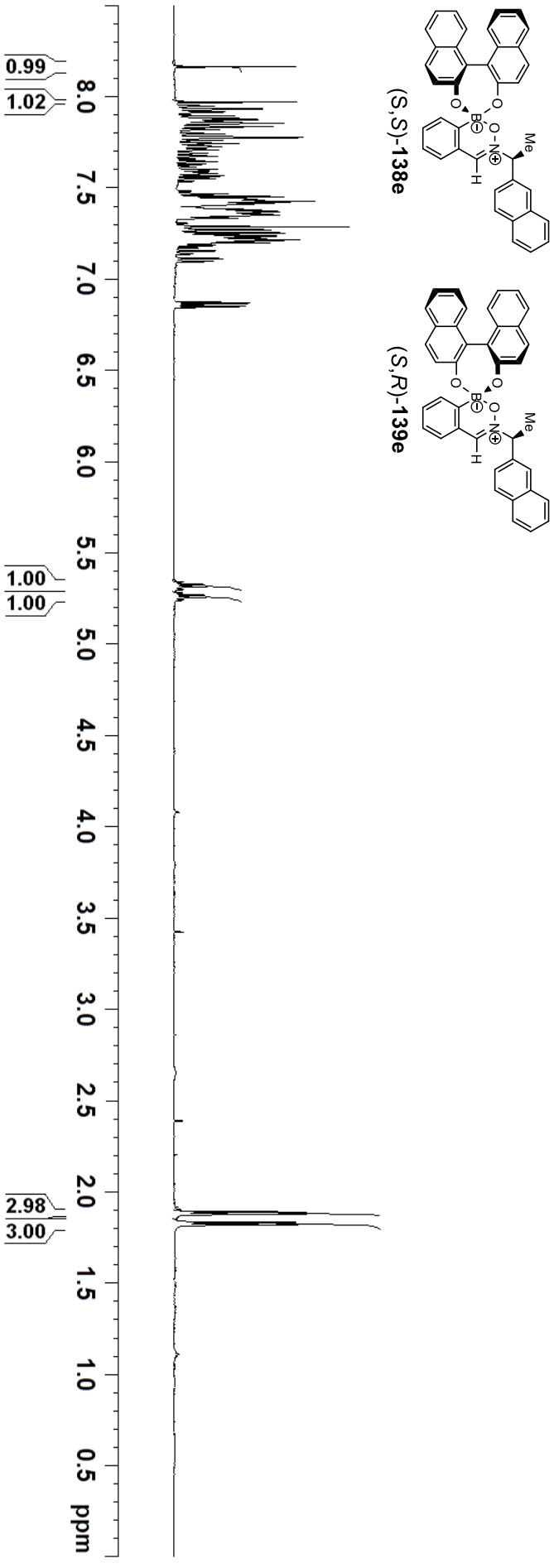
(*S*,*S*)-**138d**



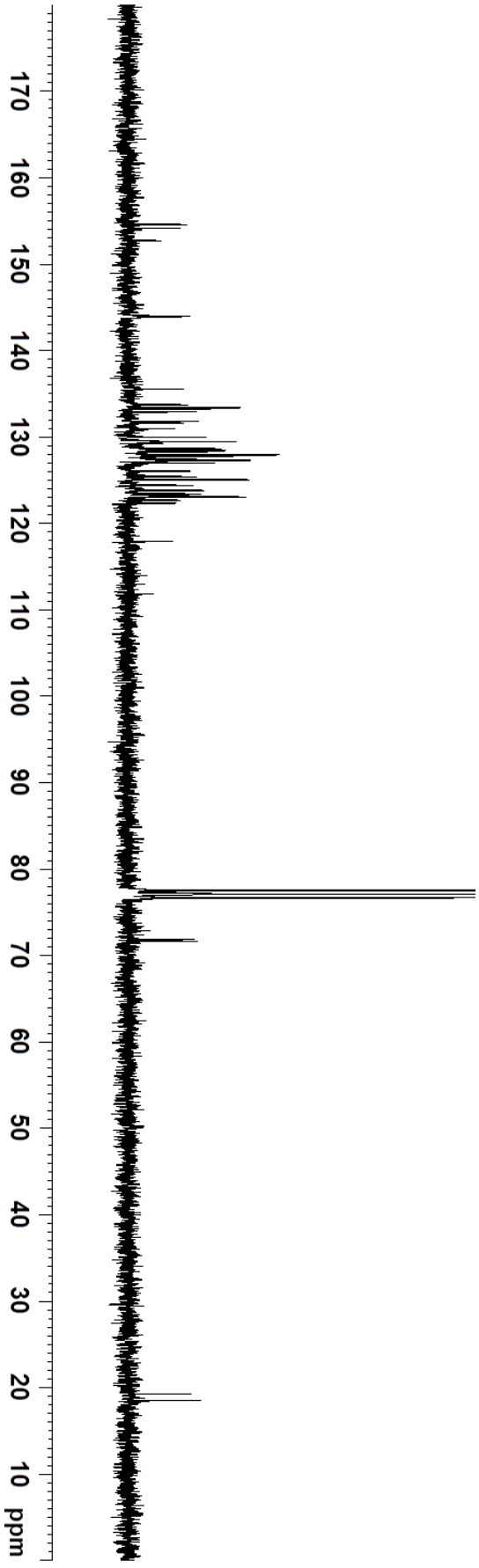
(*S*,*R*)-**139d**

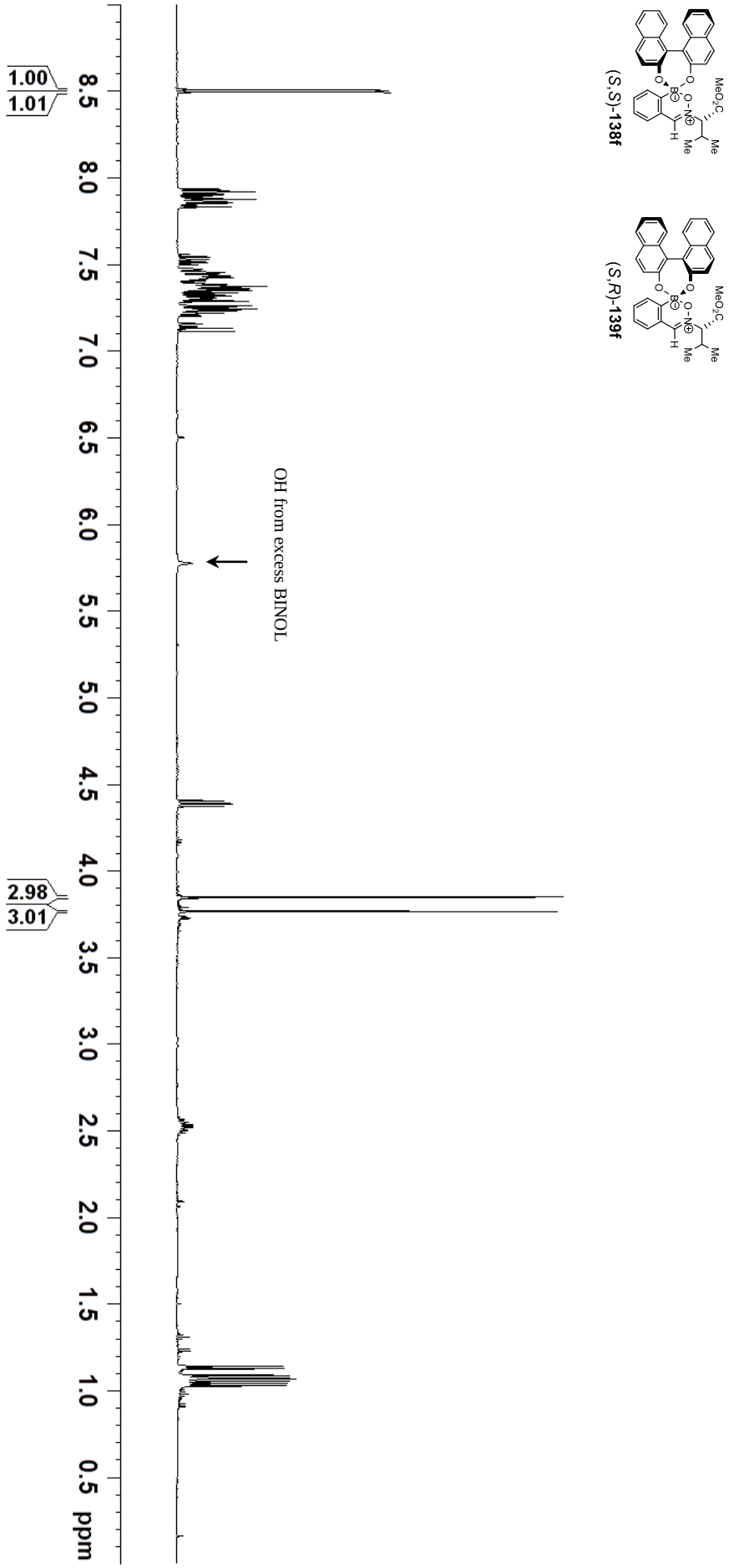


500 MHz; $CDCl_3$

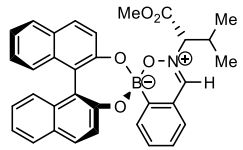


75 MHz; $CDCl_3$

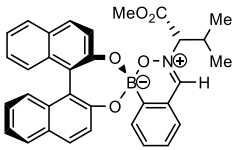

(S,S)-138e
(S,R)-139e
Me
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


500 MHz; $CDCl_3$
(*S*,*S*)-**138f**
(*S*,*R*)-**139f**
OH from excess BINOL
1.00
1.01
2.98
3.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

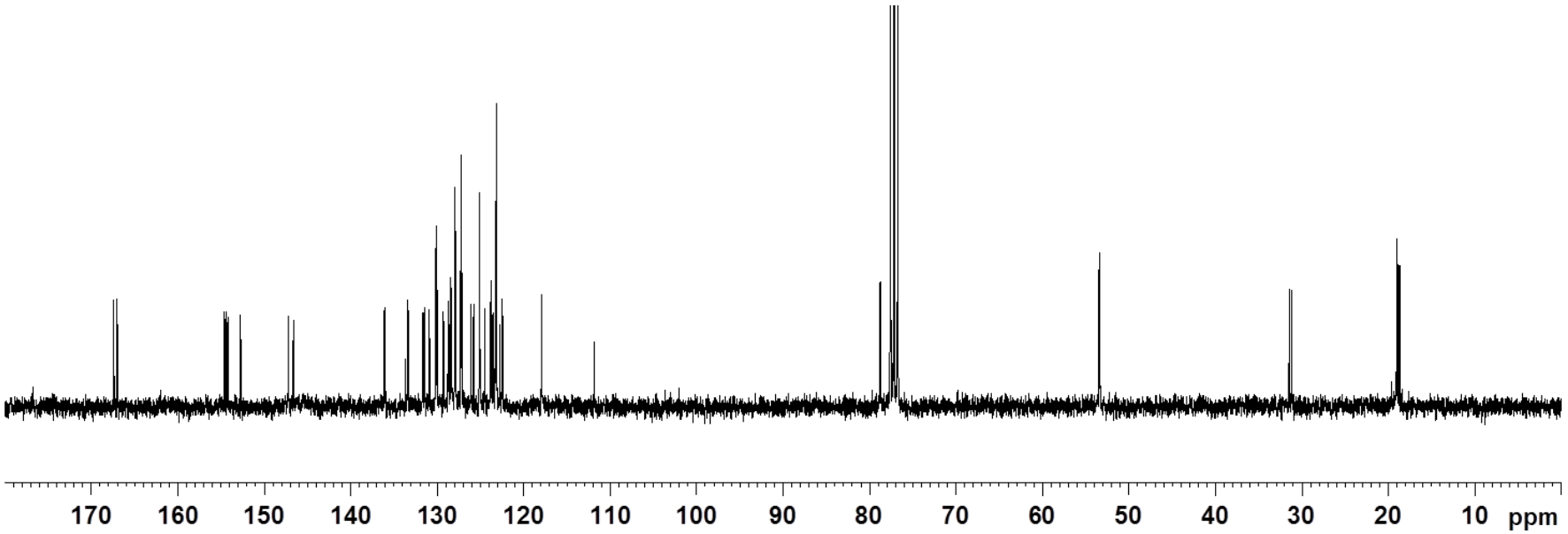
75 MHz; $CDCl_3$

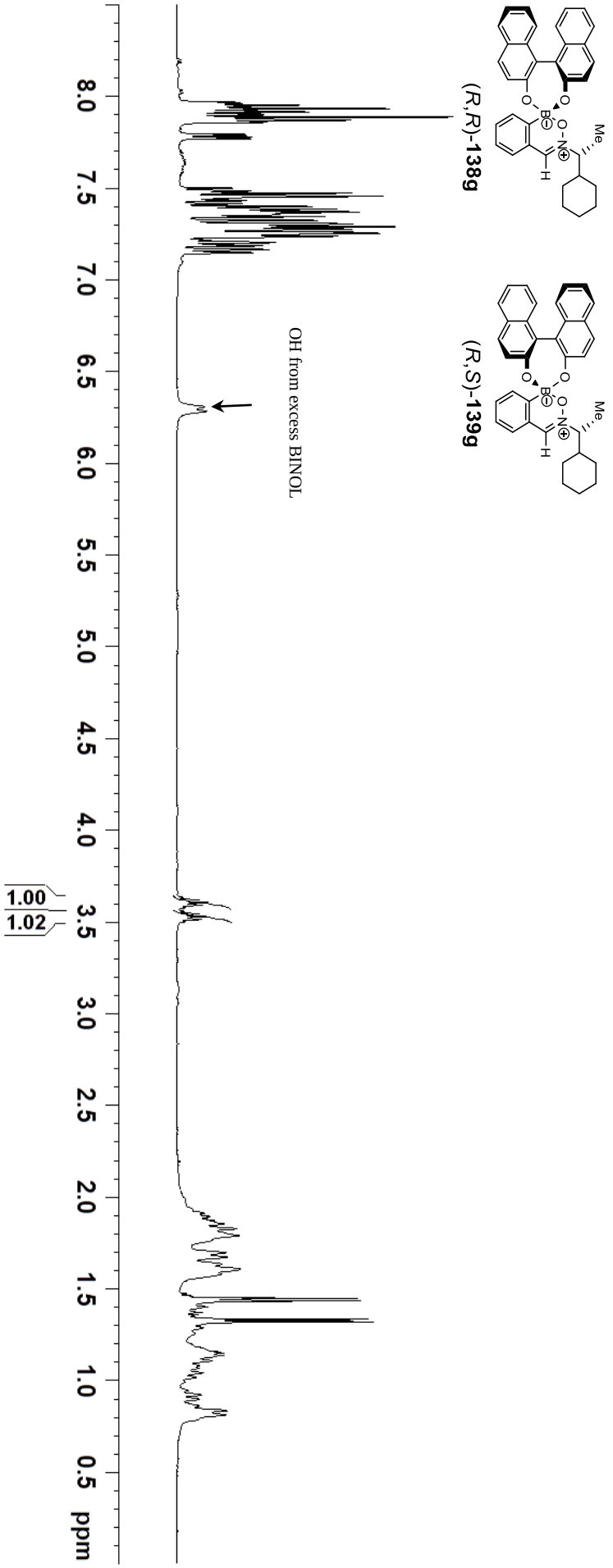


(*S*,*S*)-**138f**

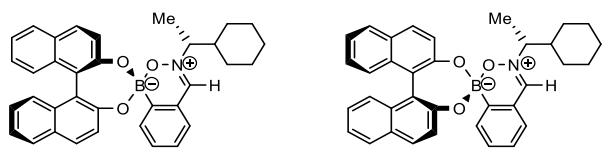


(*S*,*R*)-**139f**




500 MHz; $CDCl_3$
(*R*,*R*)-**138g**
(*R*,*S*)-**139g**
OH from excess BINOL
1.00
1.02
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

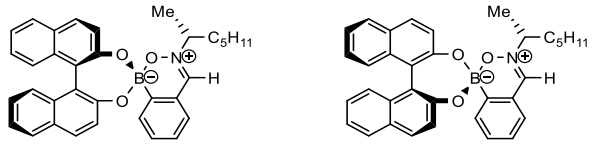
75 MHz; $CDCl_3$



(*R*,*R*)-**138g**

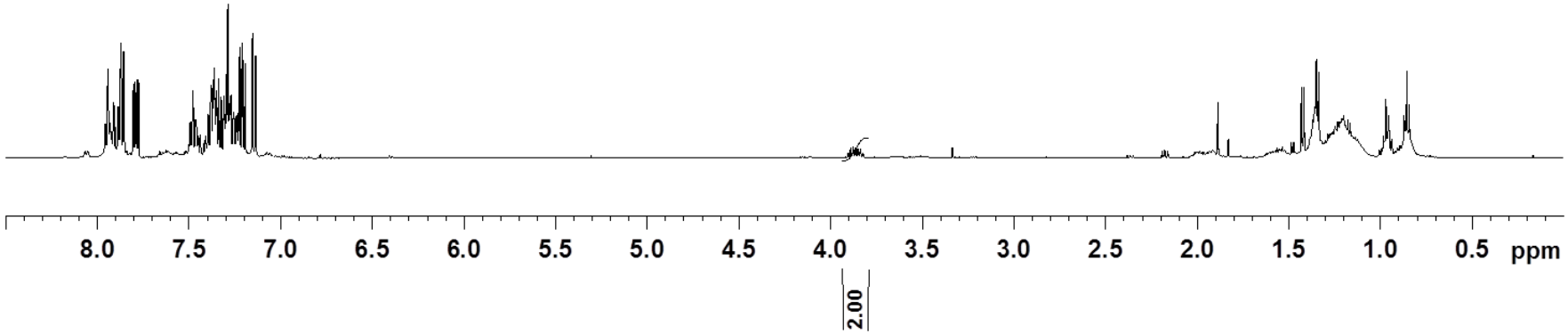
(*R*,*S*)-**139g**

500 MHz; $CDCl_3$

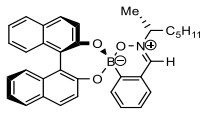


(*R*,*R*)-**138h**

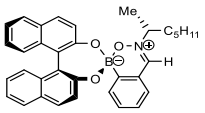
(*R*,*S*)-**139h**



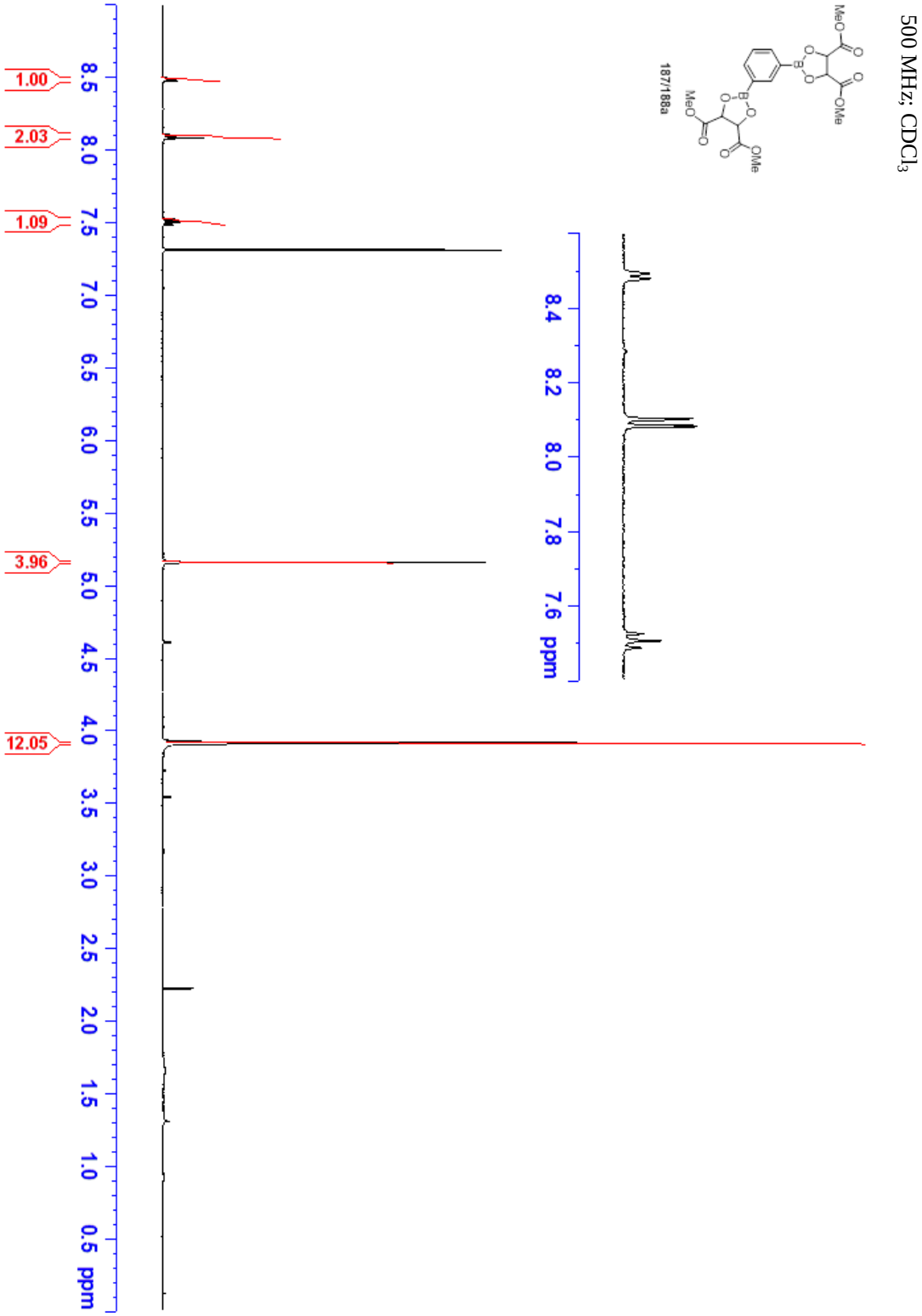
125 MHz; $CDCl_3$



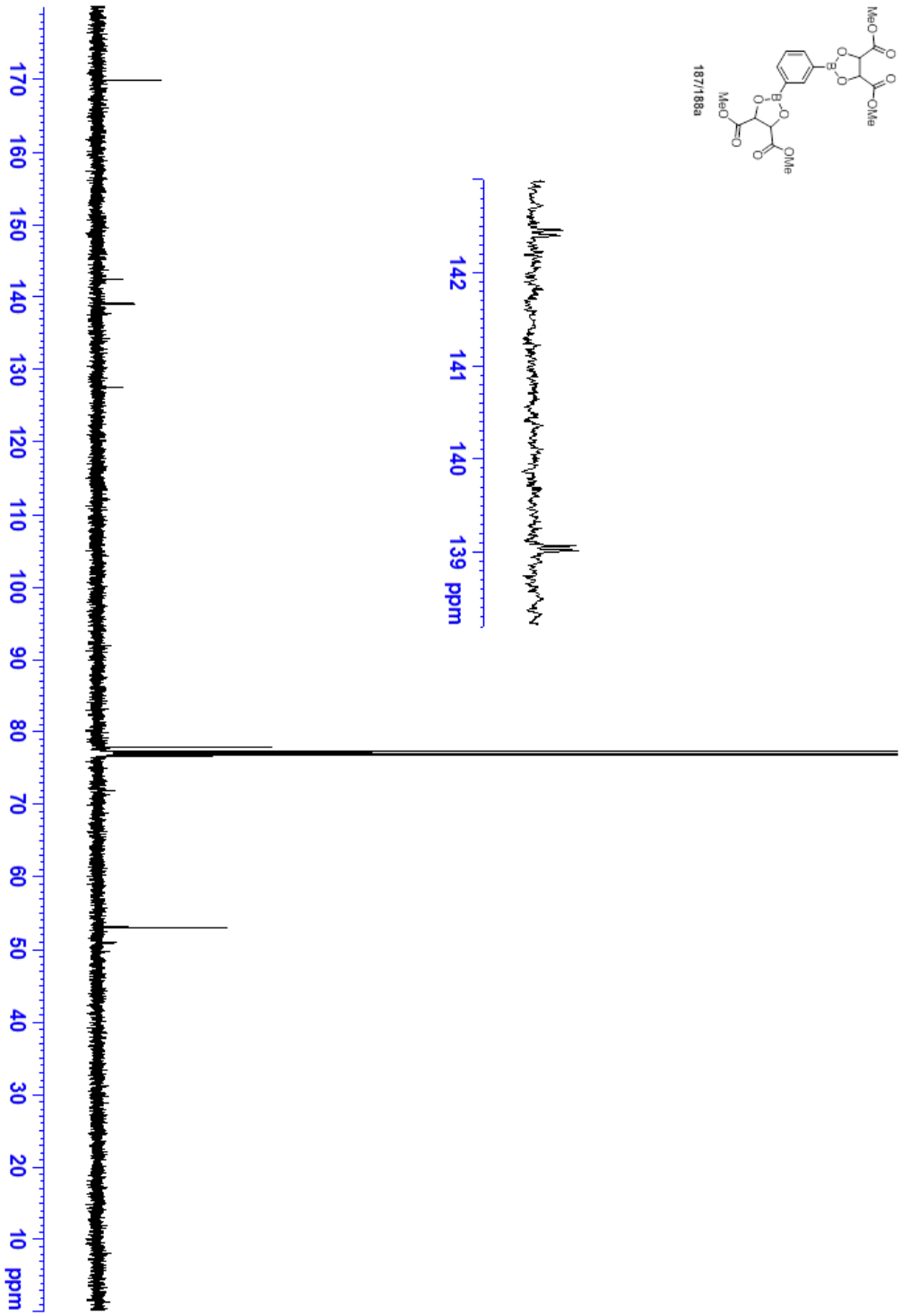
(*R*,*R*)-**138h**

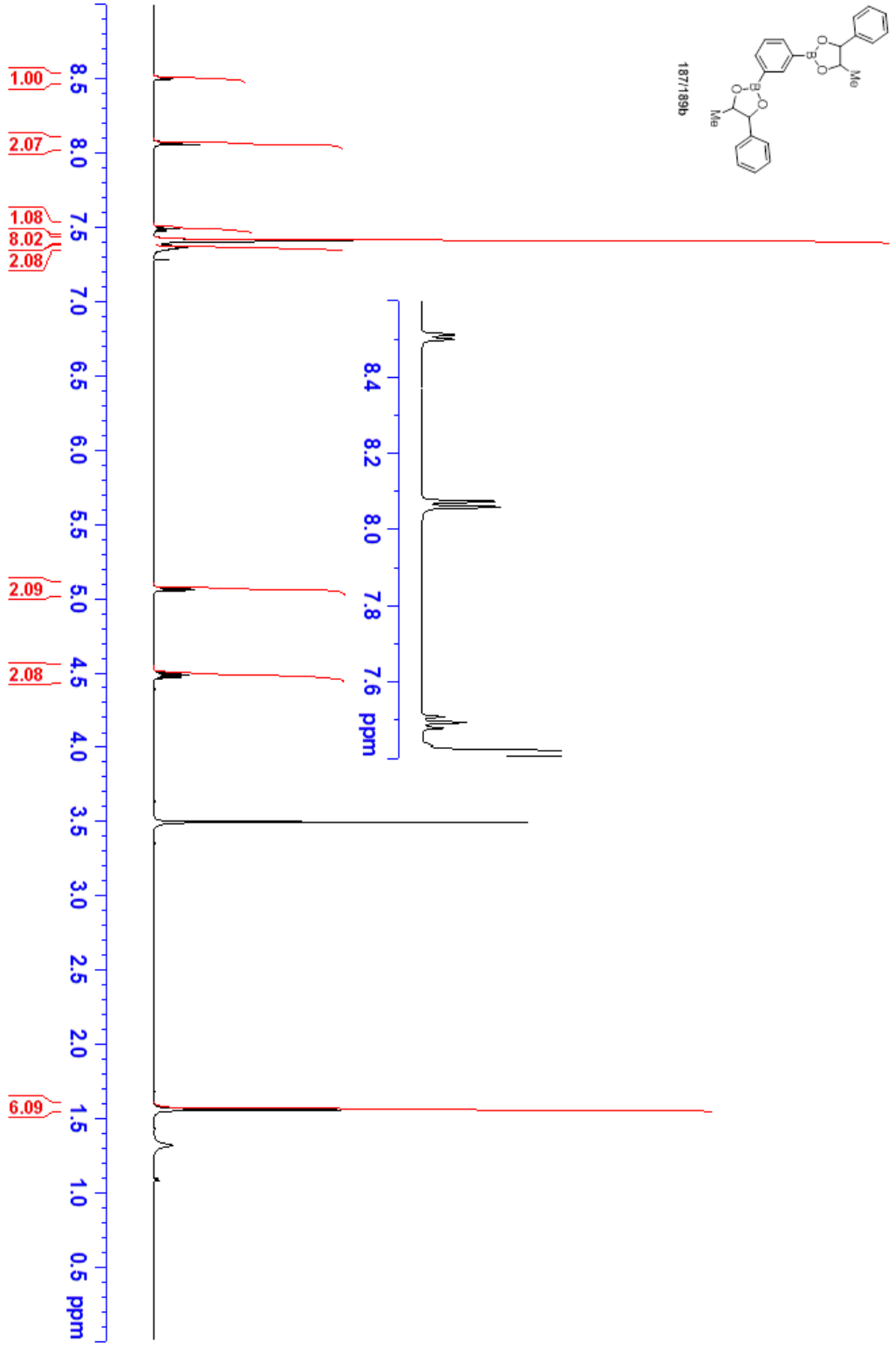


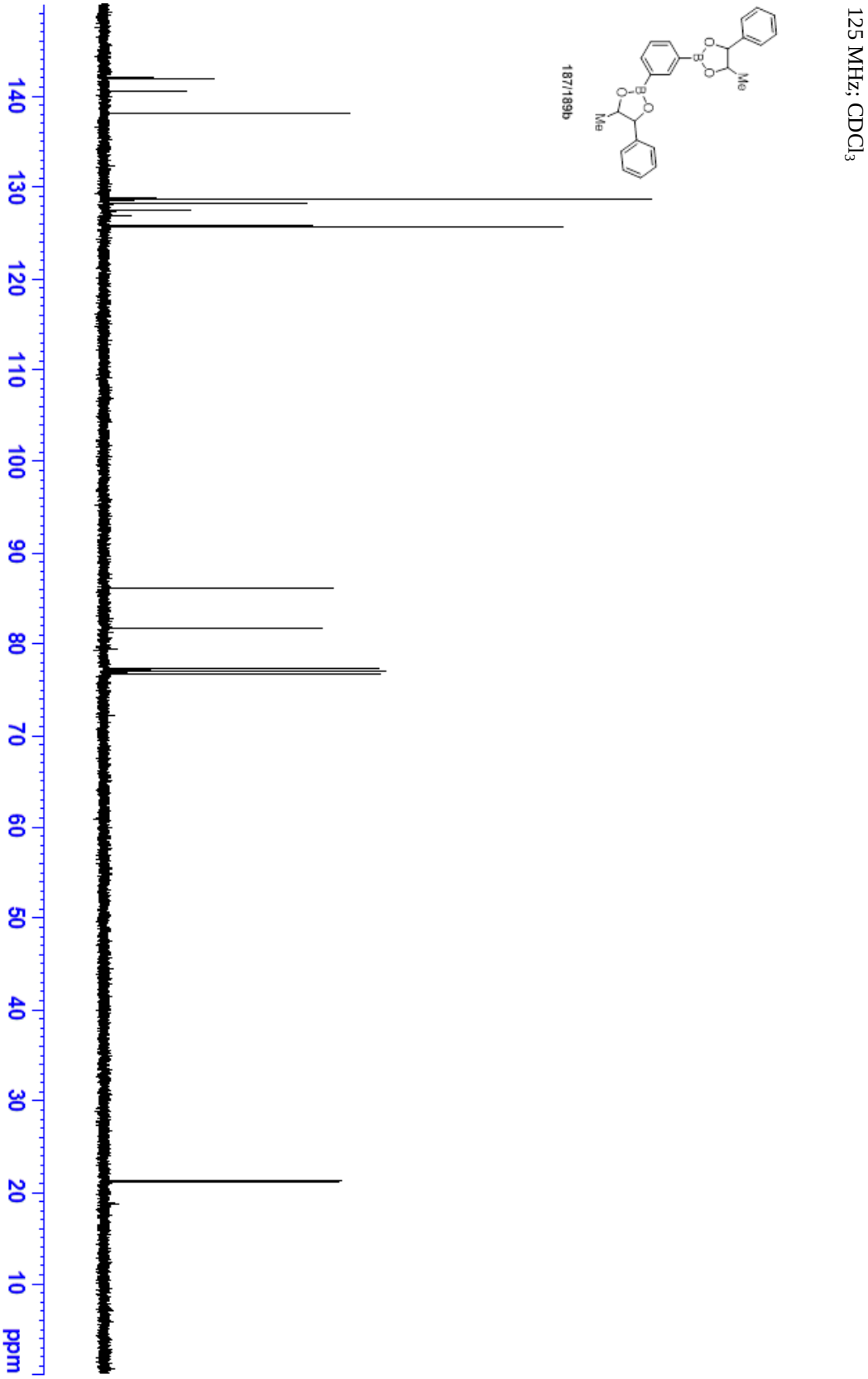
(*R*,*S*)-**139h**


500 MHz; $CDCl_3$
187/188a
MeO
OMe
1.00
2.03
1.09
3.96
12.05
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
8.4 8.2 8.0 7.8 7.6 ppm

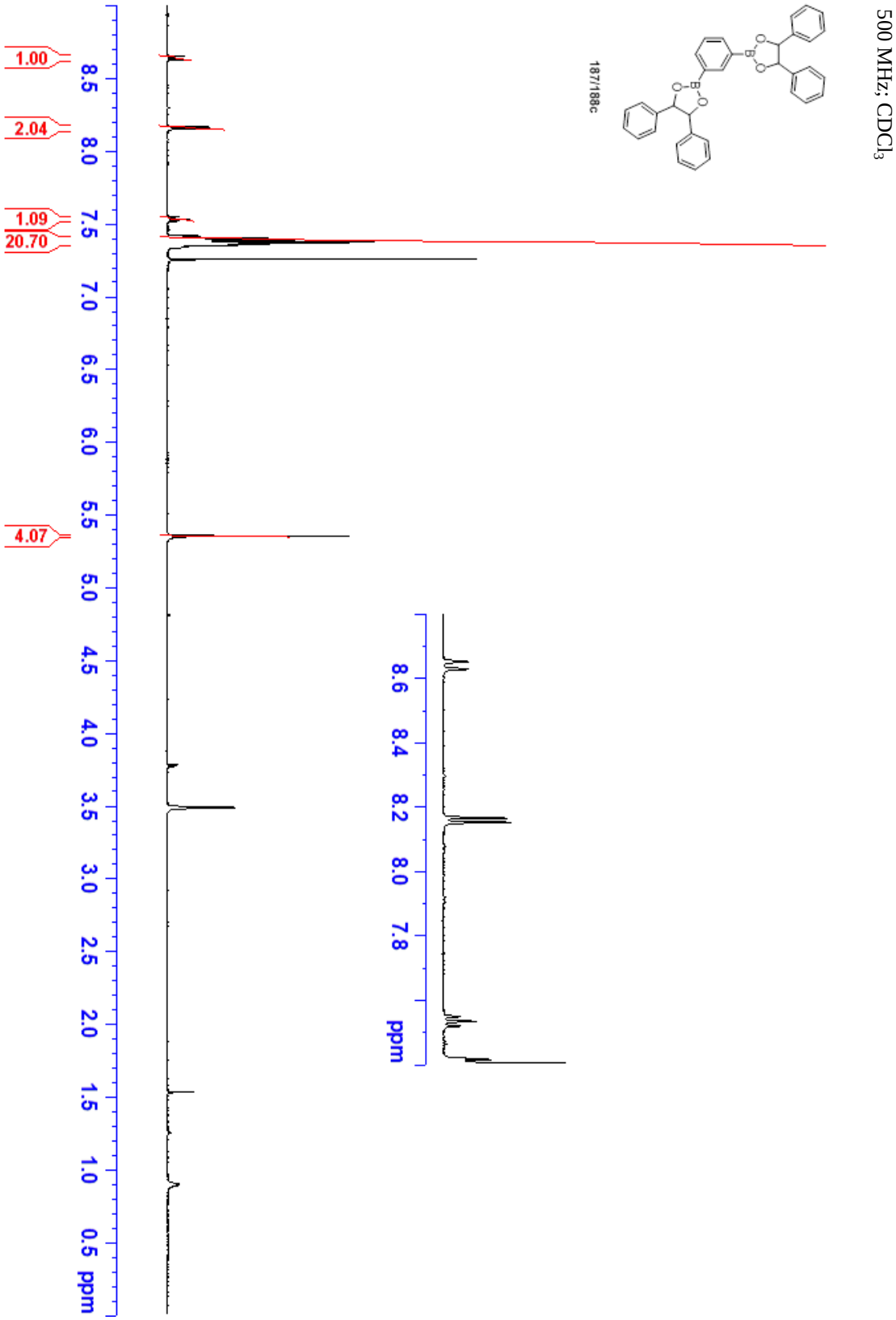
125 MHz; $CDCl_3$

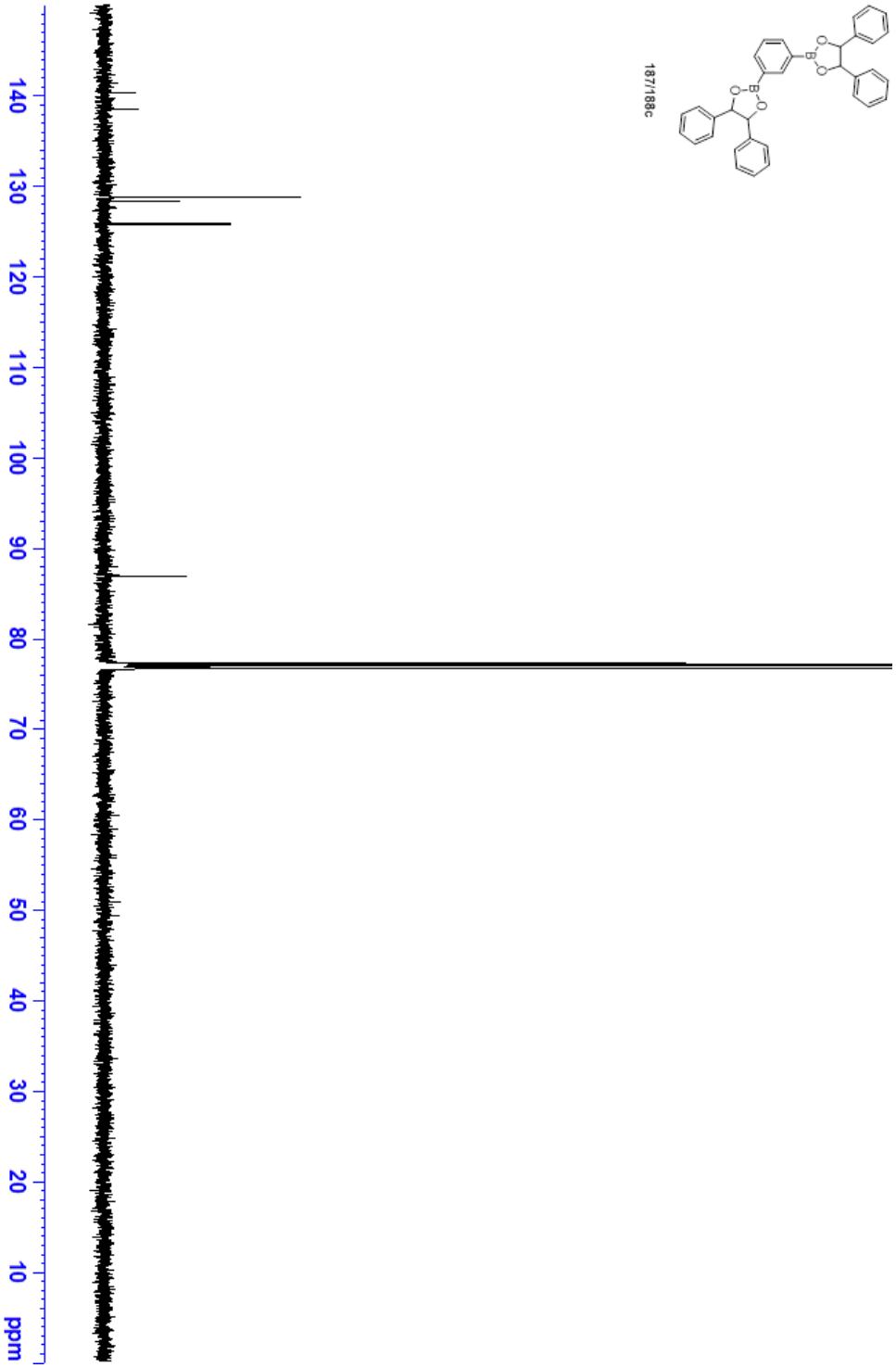



500 MHz; $CDCl_3$
187/189b
Me
Me
1.00
2.07
1.08
8.02
2.08
2.09
2.08
6.09
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
8.4
8.2
8.0
7.8
7.6
ppm

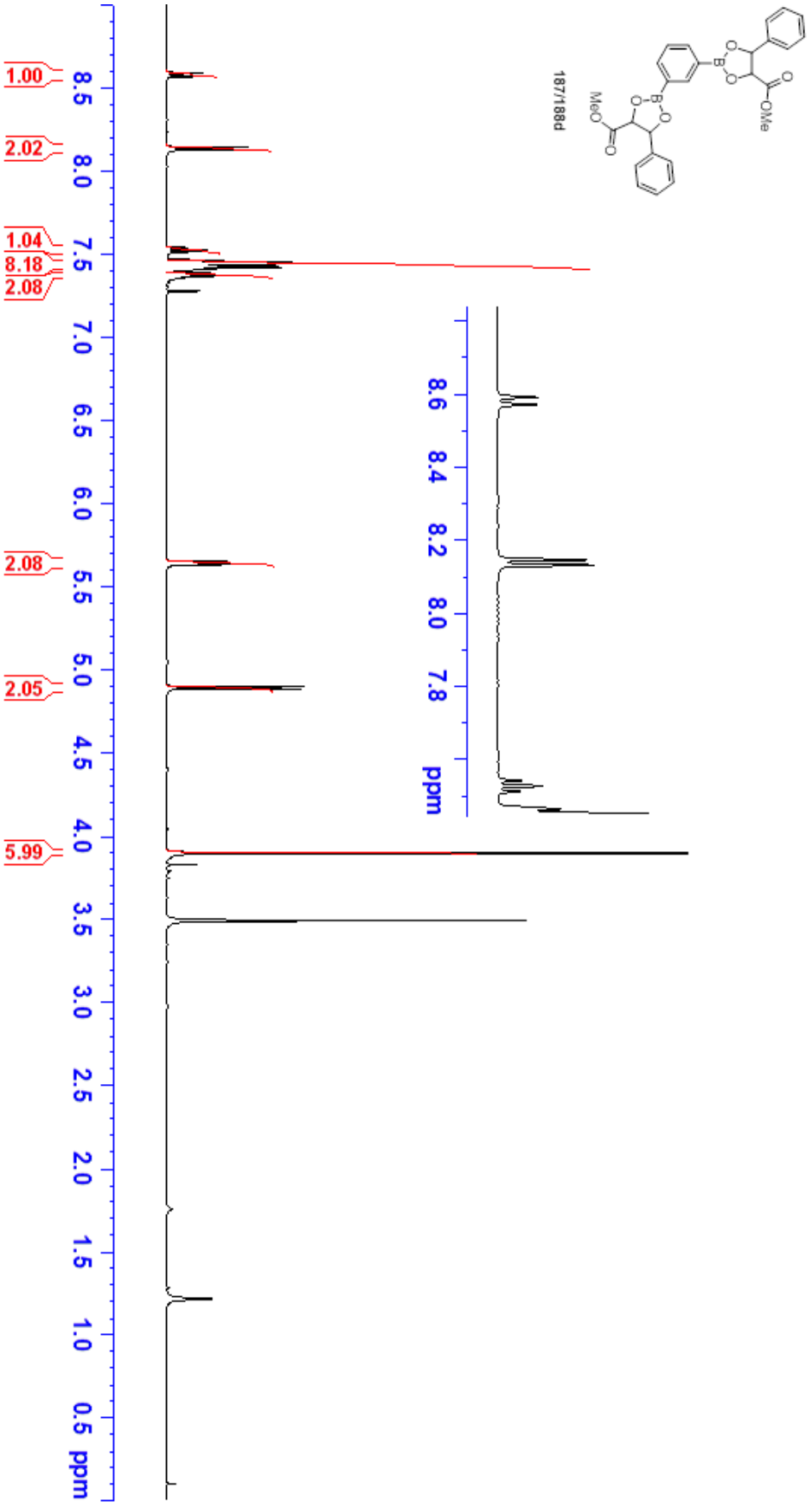


125 MHz; $CDCl_3$

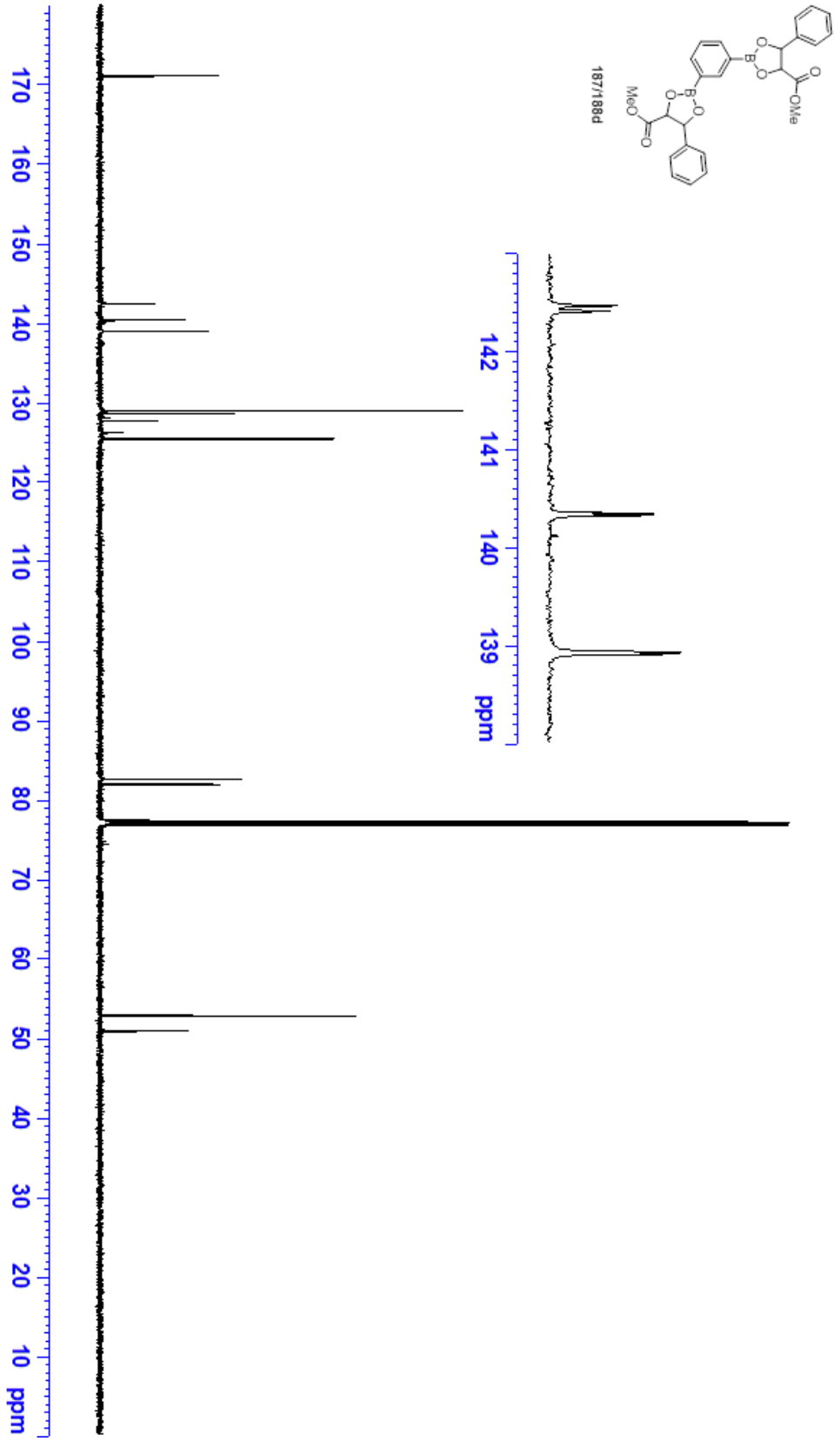

500 MHz; $CDCl_3$
187/188c
1.00
2.04
1.09
20.70
4.07
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
8.6
8.4
8.2
8.0
7.8
ppm

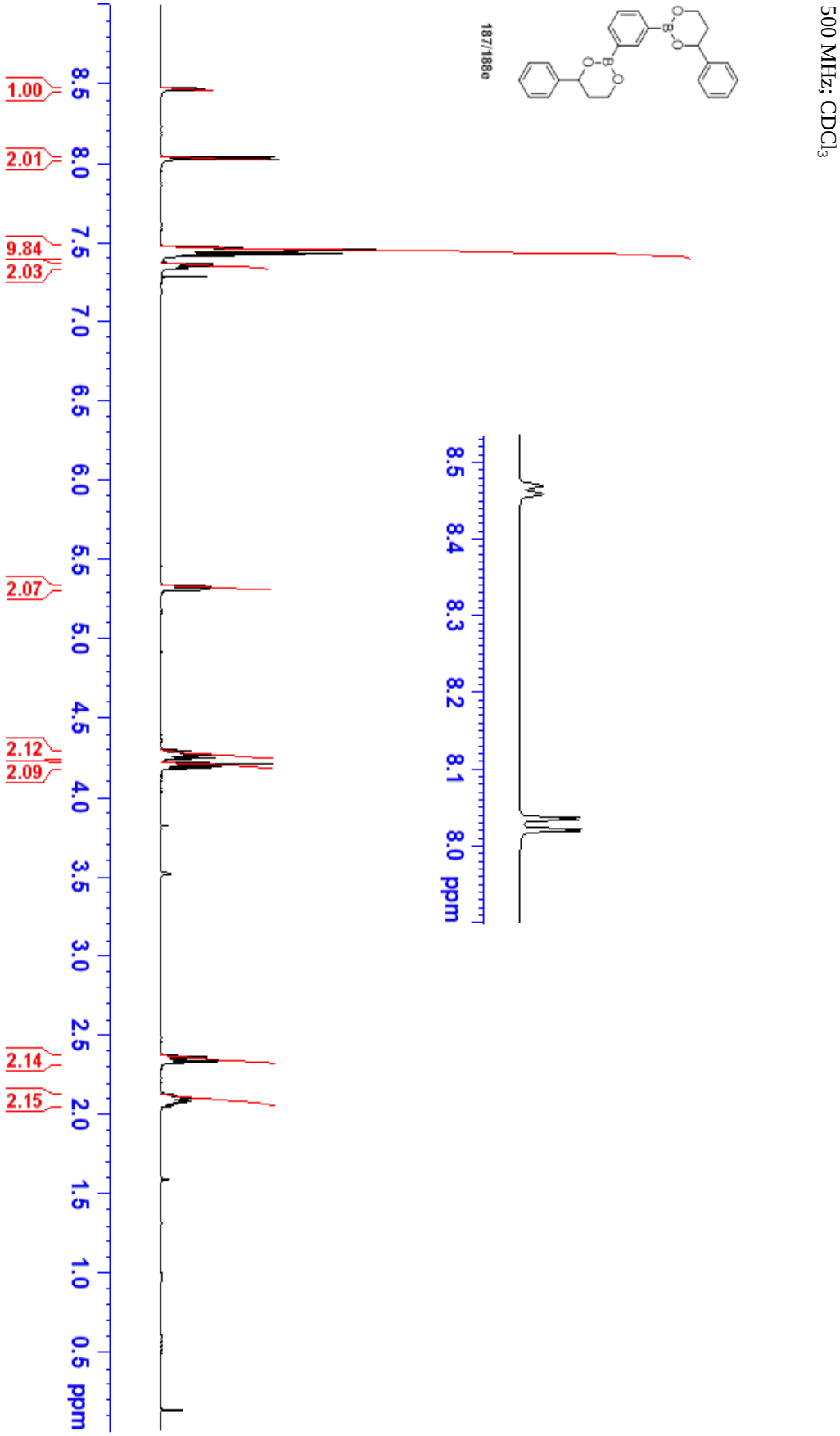

125 MHz; $CDCl_3$
187/188c
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

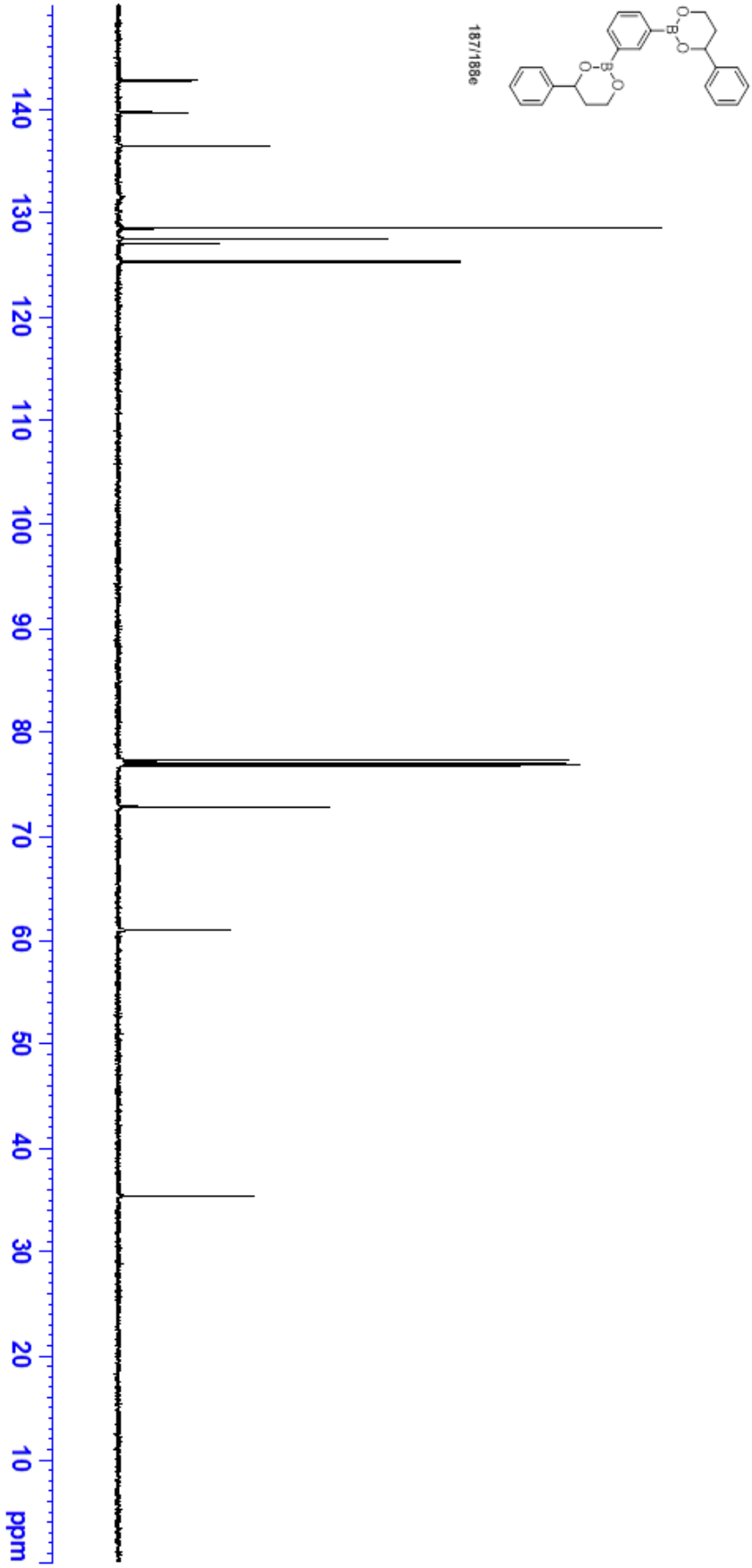
500 MHz; $CDCl_3$



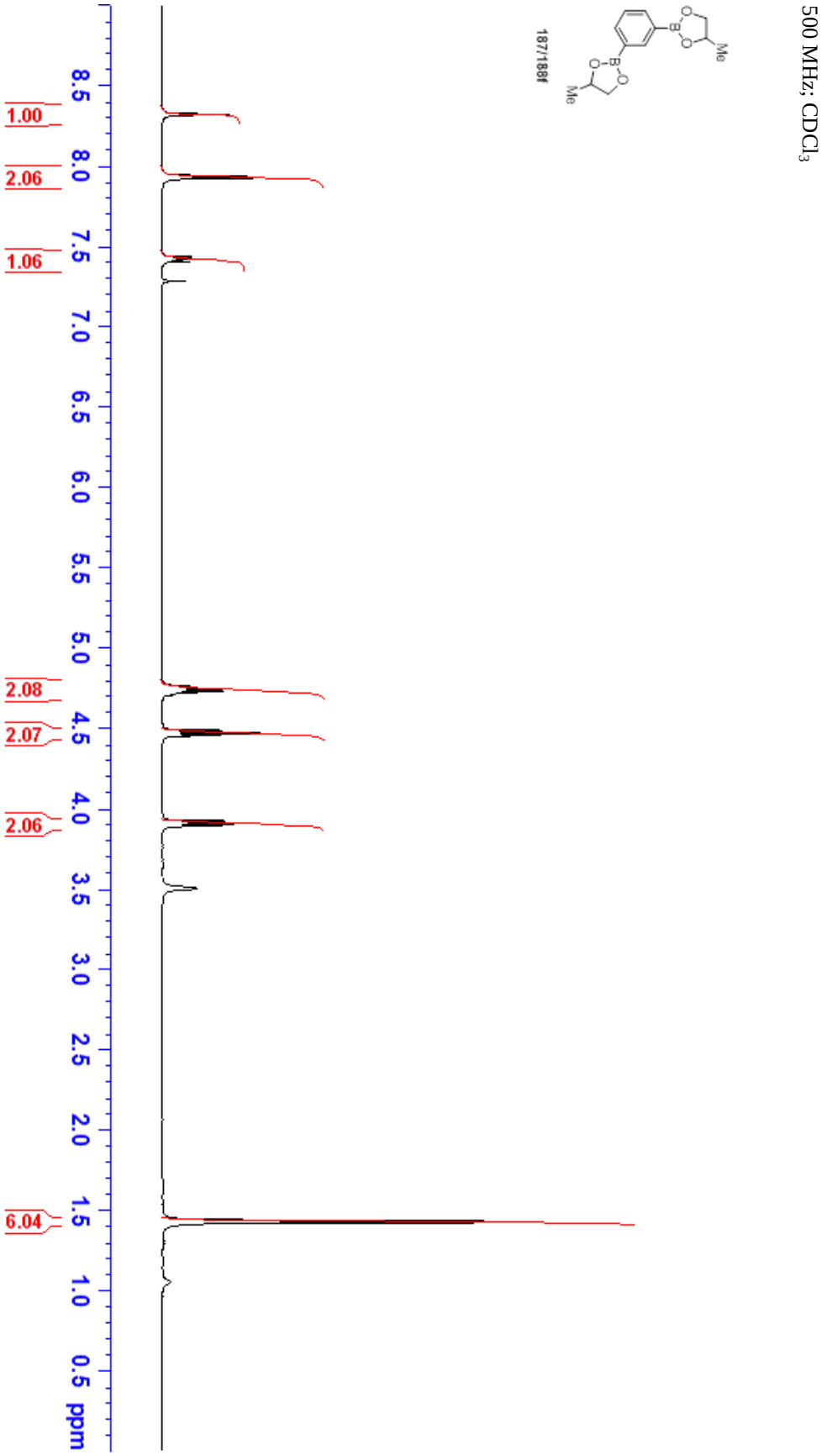
125 MHz; $CDCl_3$

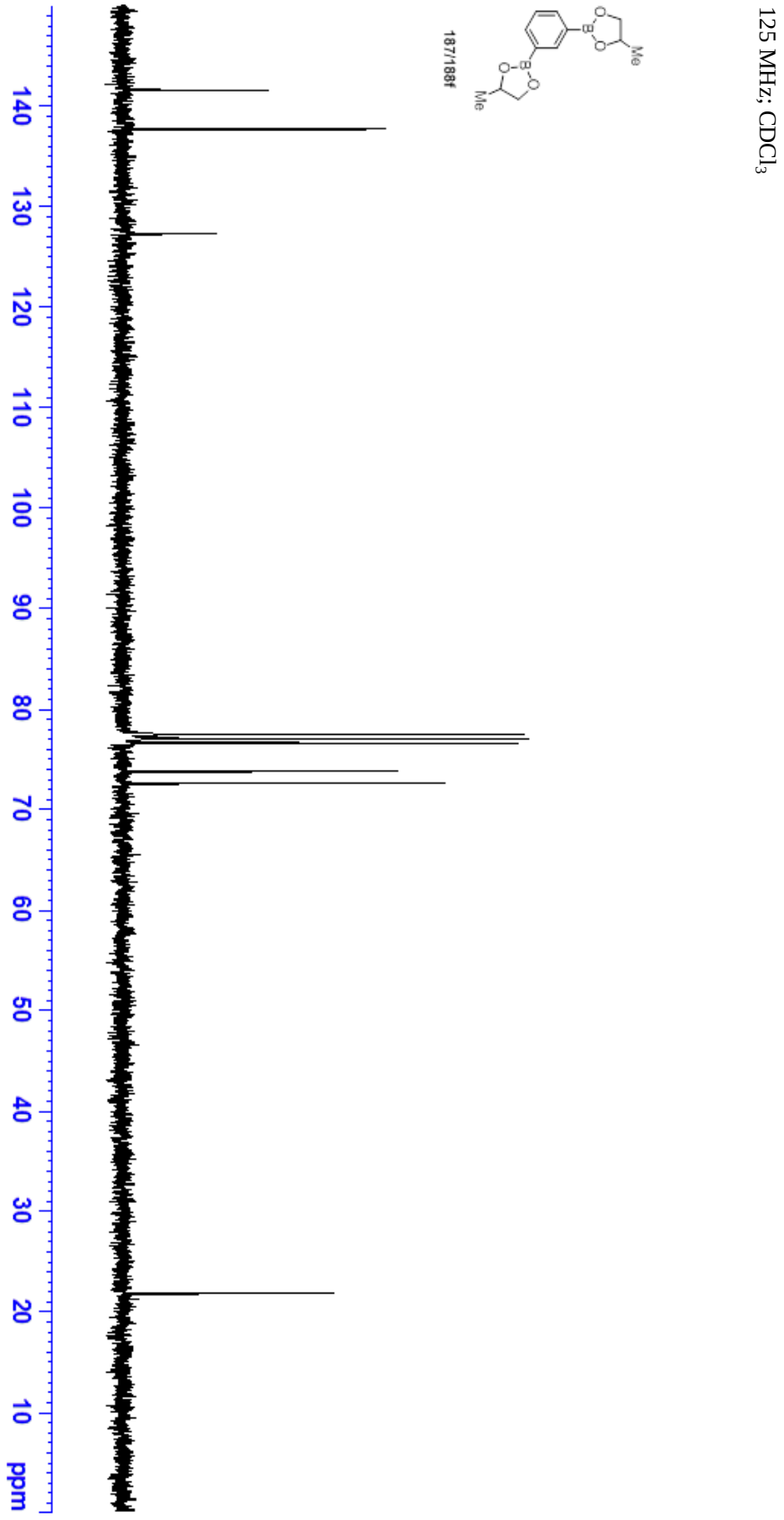



500 MHz; $CDCl_3$
187/188e
1.00
2.01
9.84
2.03
2.07
2.12
2.09
2.14
2.15
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
8.5 8.4 8.3 8.2 8.1 8.0 ppm

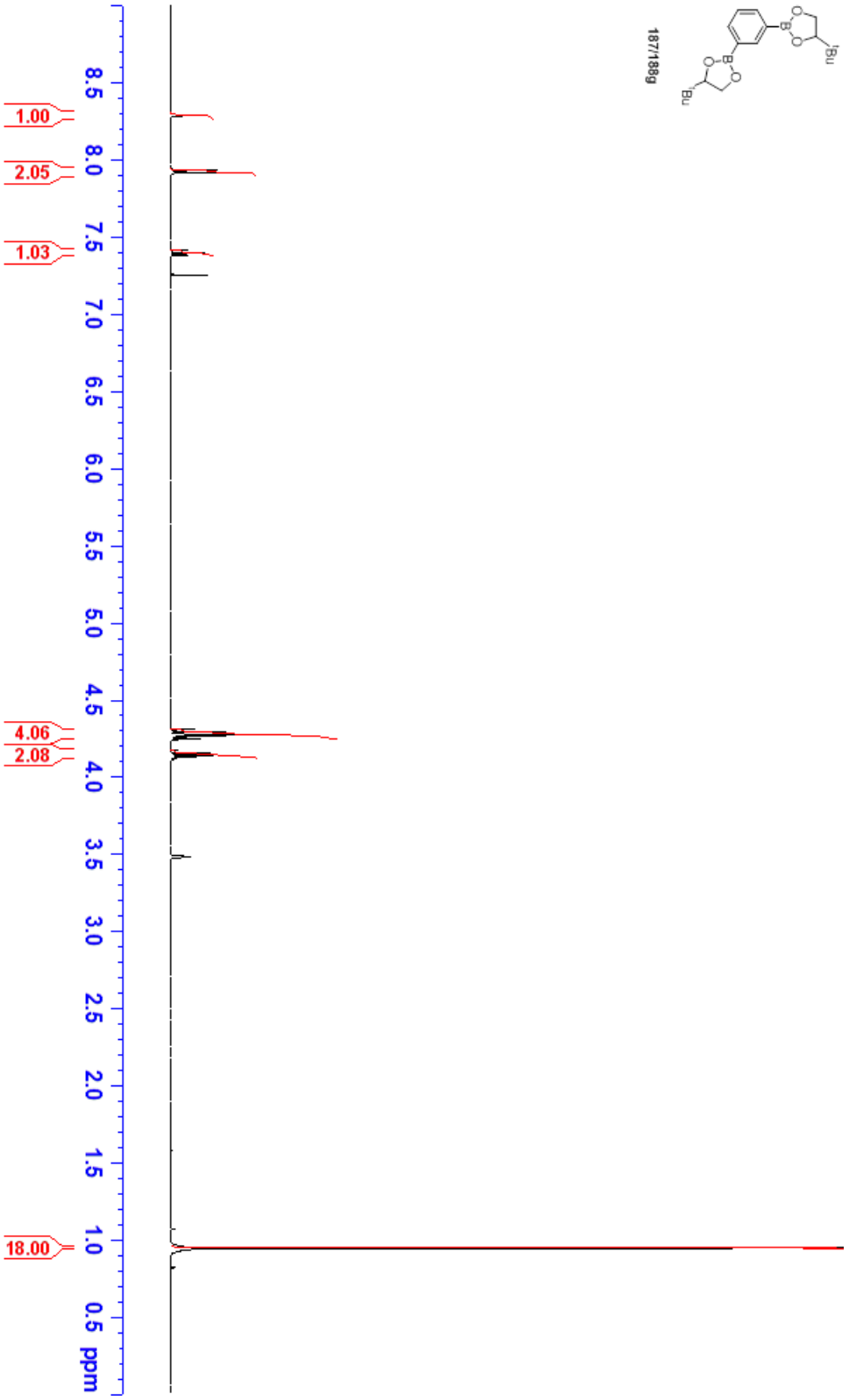


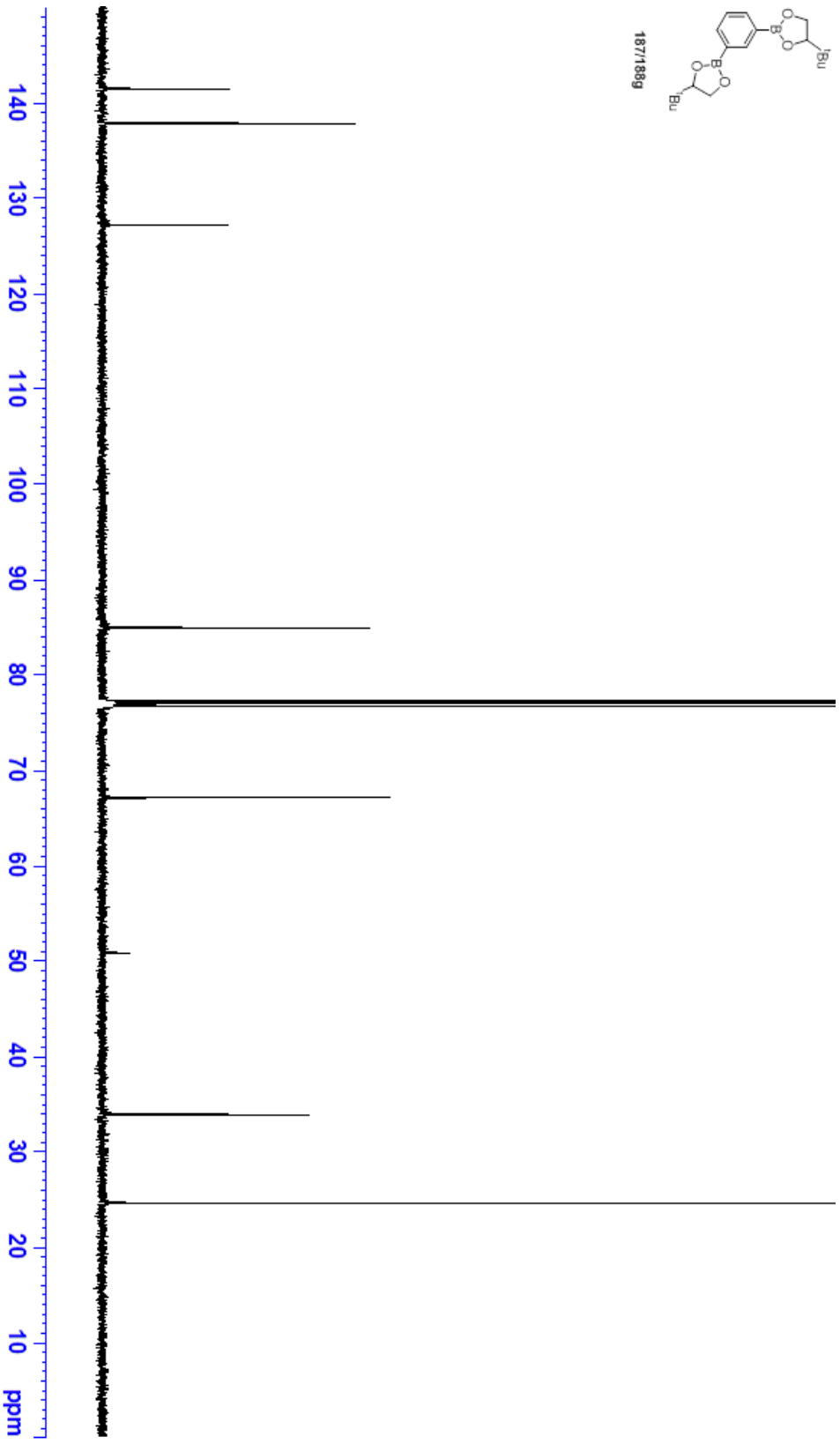
125 MHz; $CDCl_3$


500 MHz; $CDCl_3$
187/188f
Me
Me
1.00
2.06
1.06
2.08
2.07
2.06
6.04
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

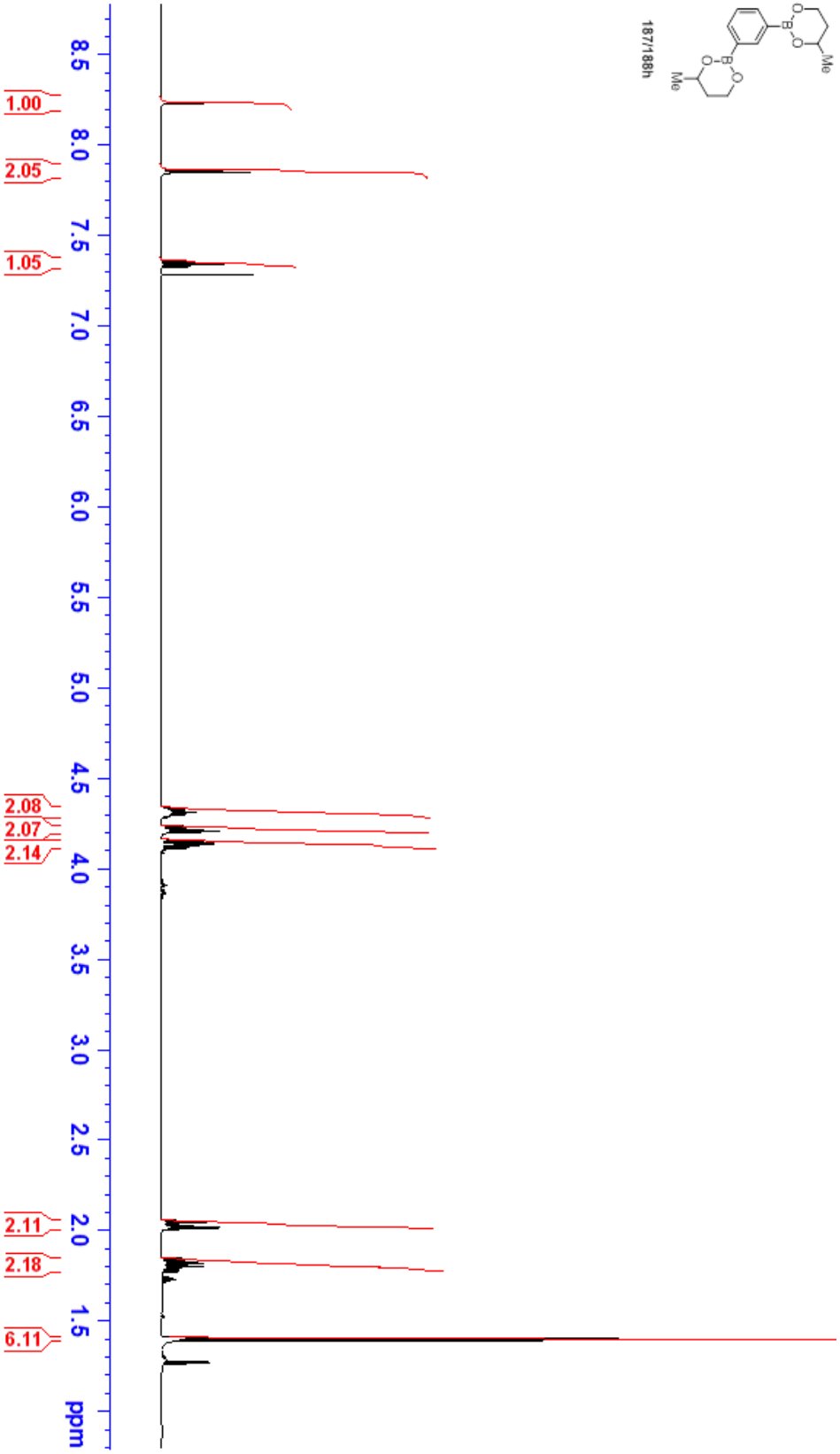


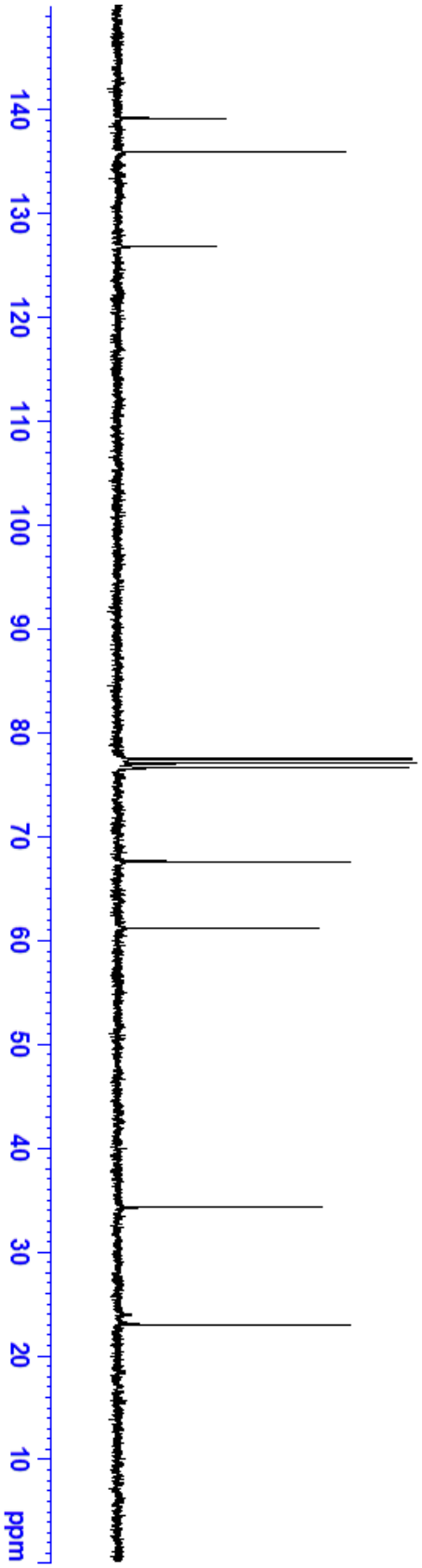
125 MHz; $CDCl_3$


500 MHz; $CDCl_3$
187/188g
1.00
2.05
1.03
4.06
2.08
18.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

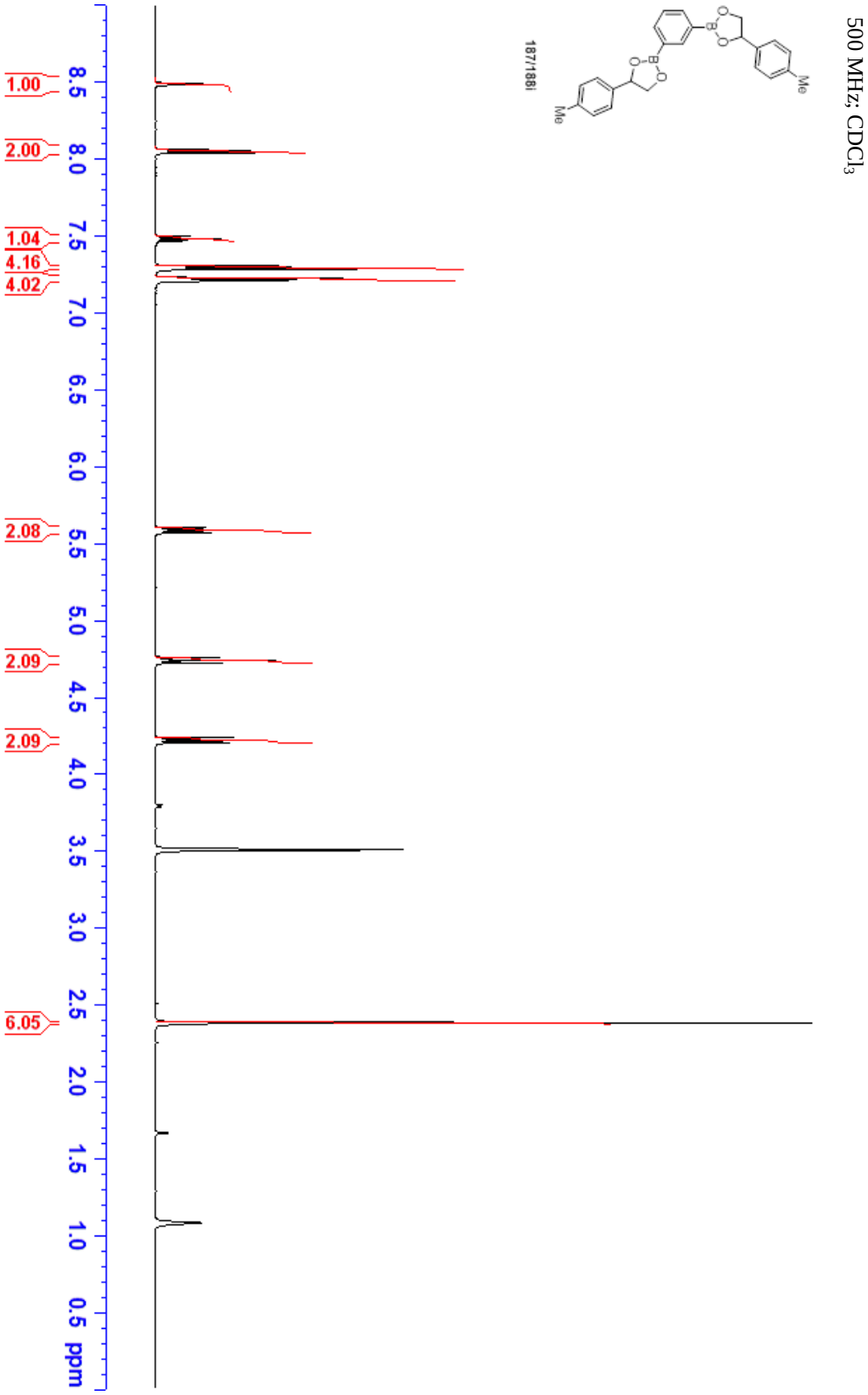


125 MHz; $CDCl_3$

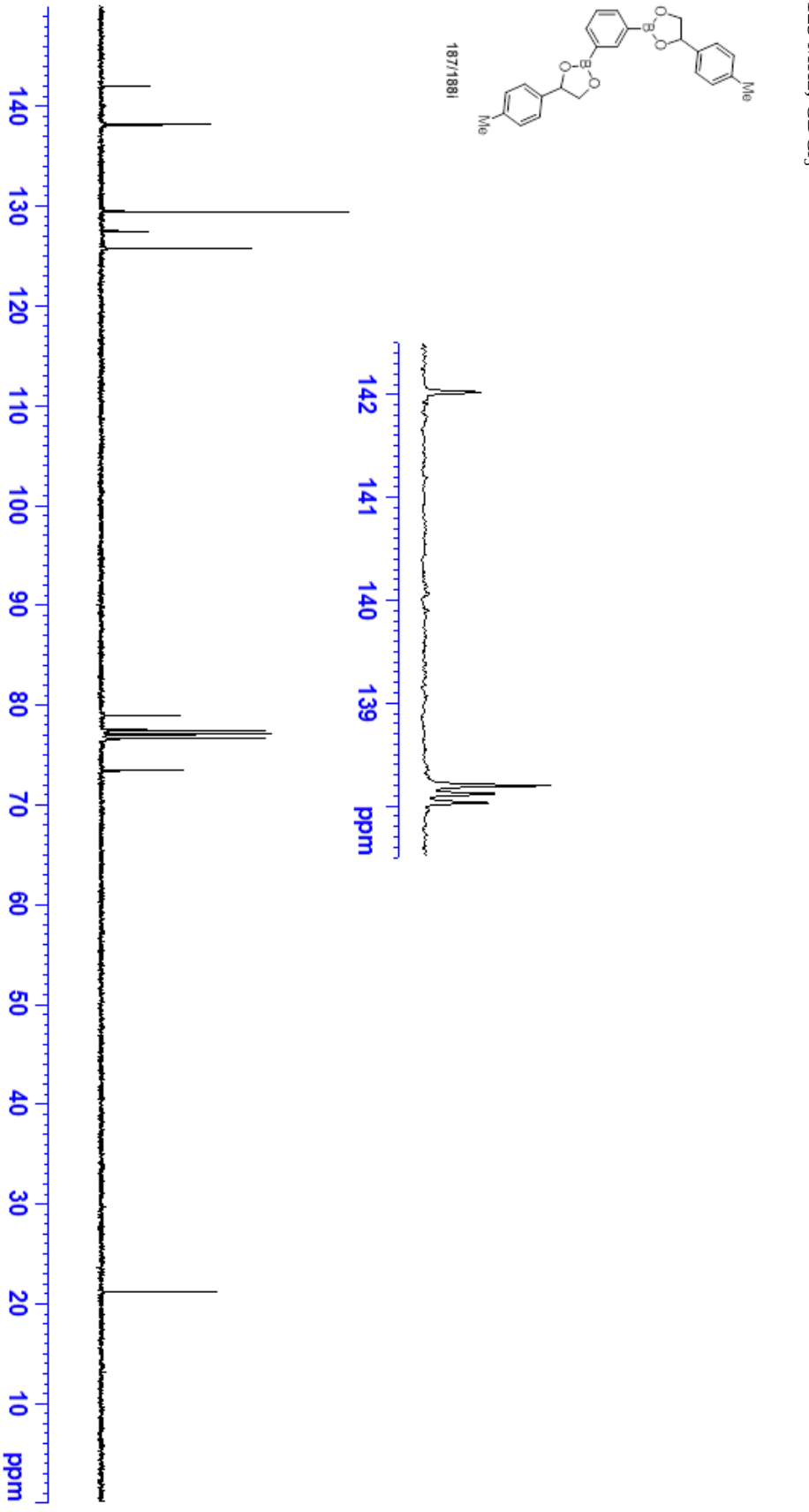

500 MHz; $CDCl_3$
187/188h
Me
Me
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.00
2.05
1.05
2.08
2.07
2.14
2.11
2.18
6.11

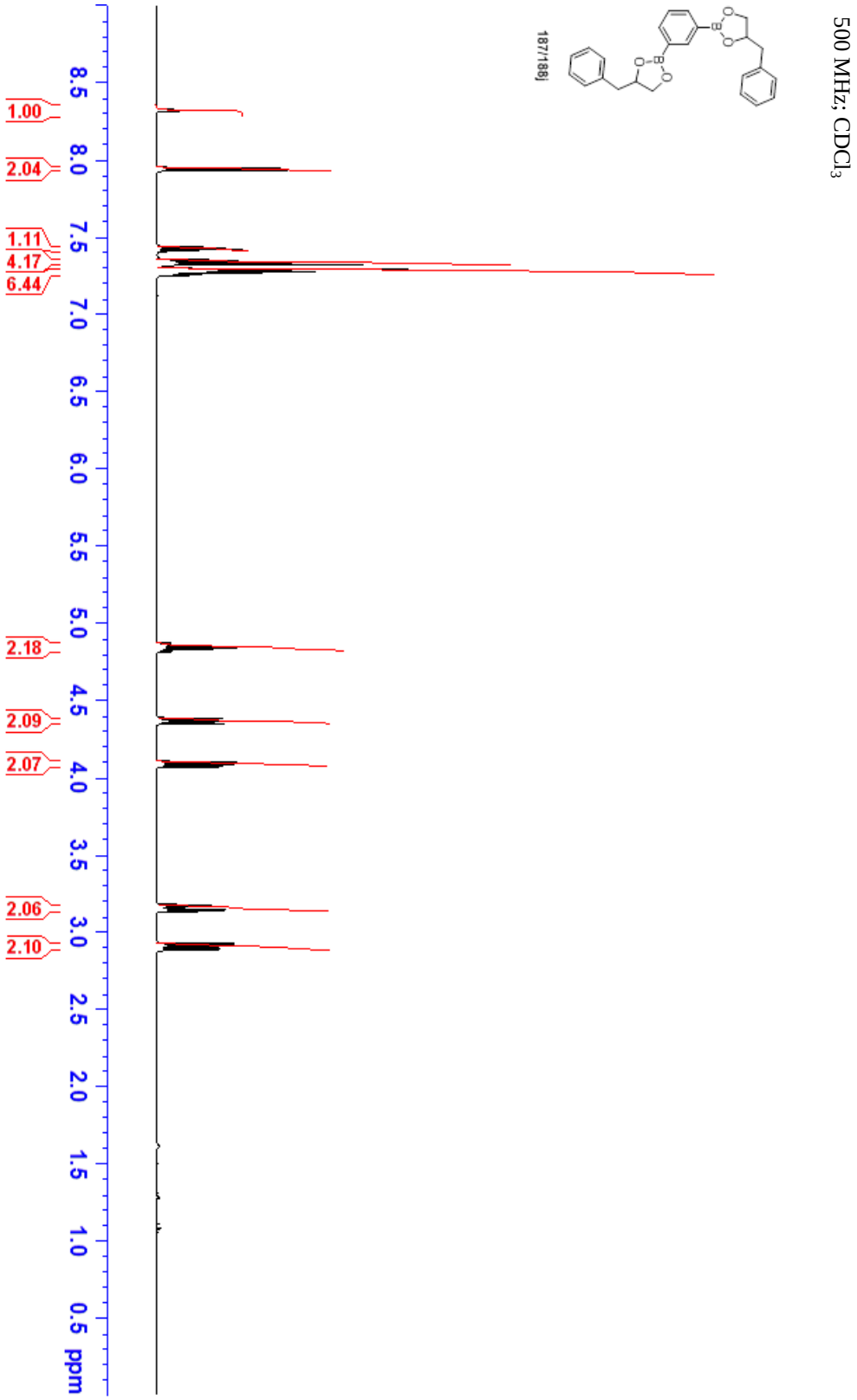


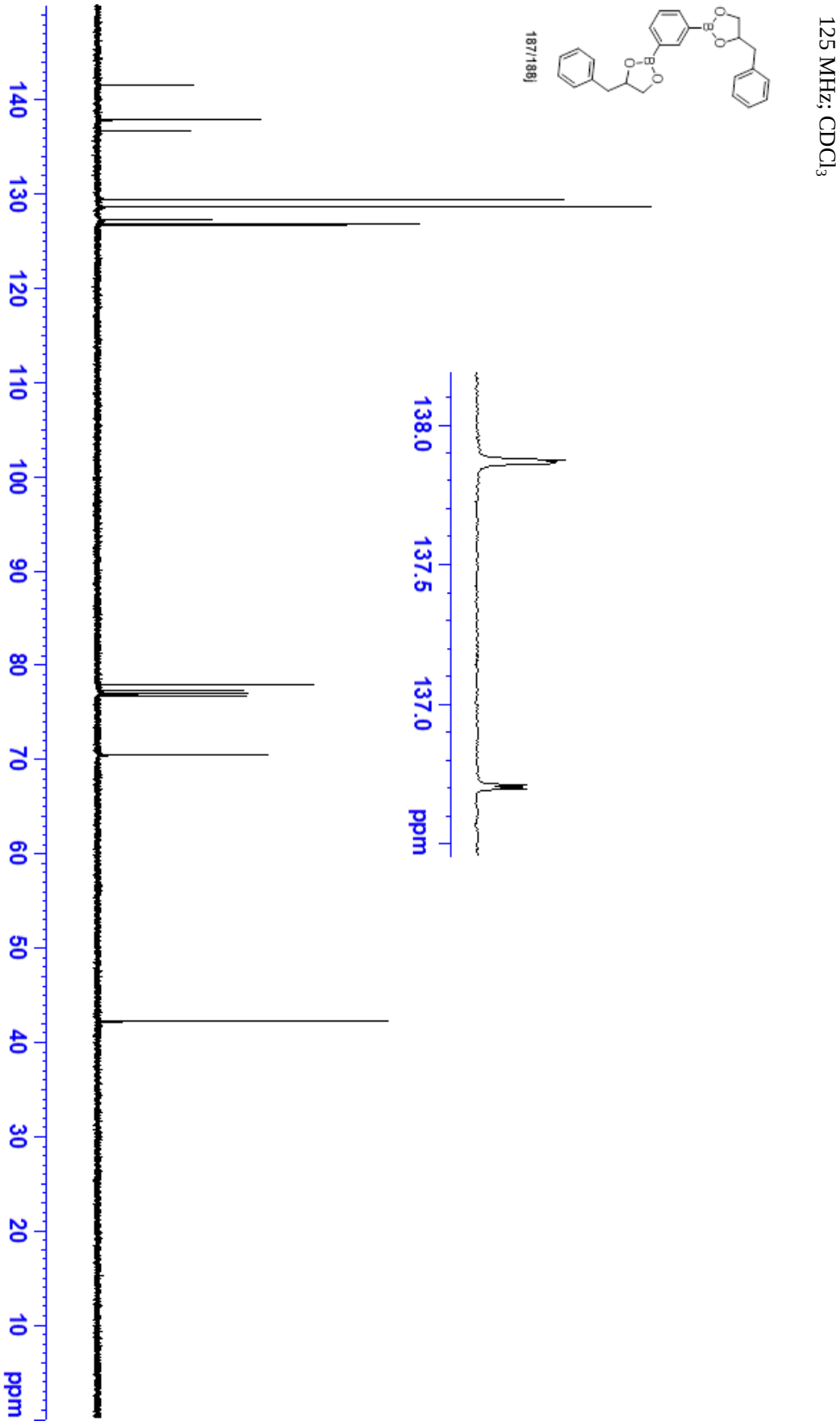
125 MHz; $CDCl_3$

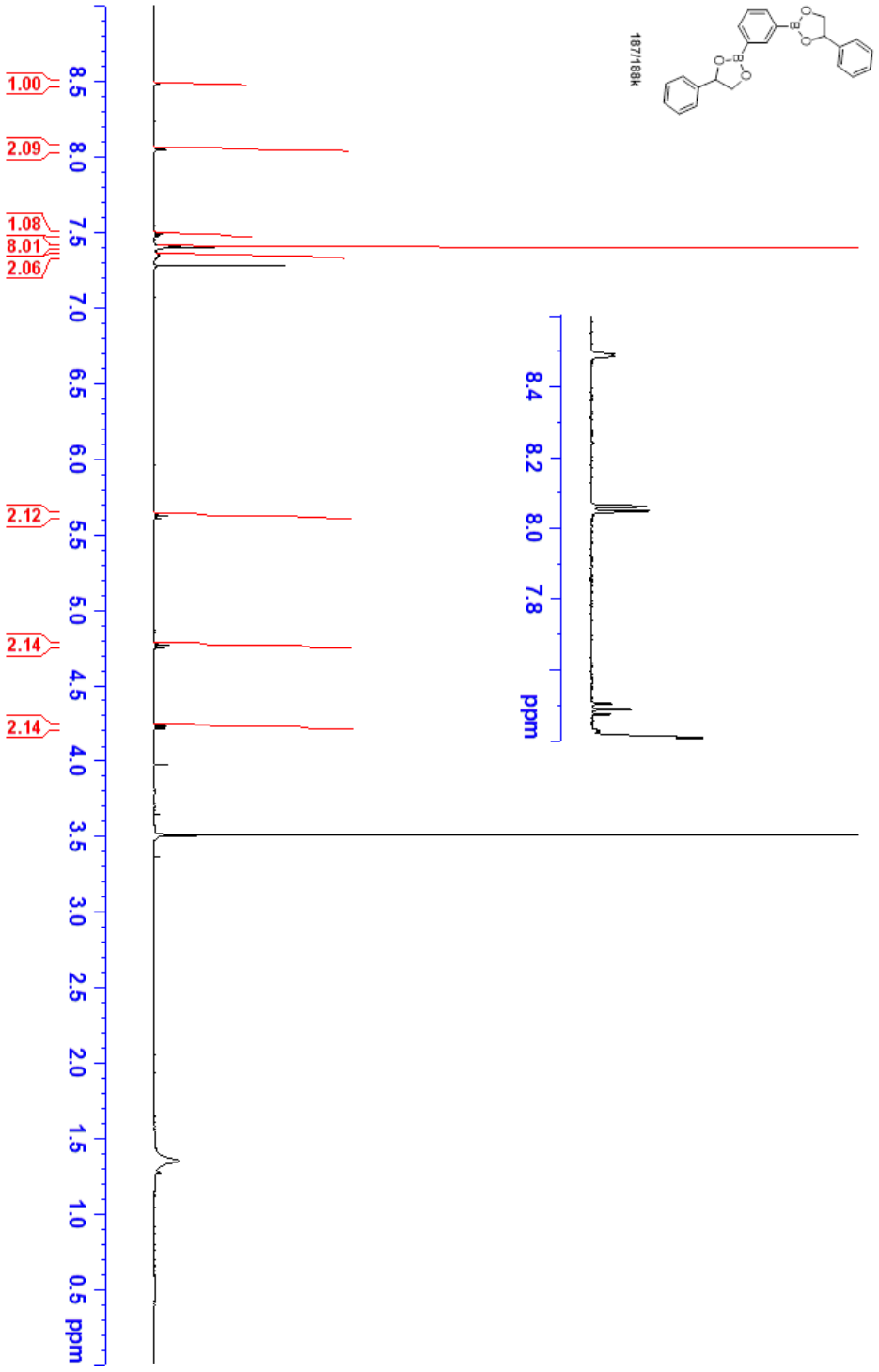

500 MHz; $CDCl_3$
187/188i
Me
Me
1.00
2.00
1.04
4.16
4.02
2.08
2.09
2.09
6.05
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

125 MHz; $CDCl_3$

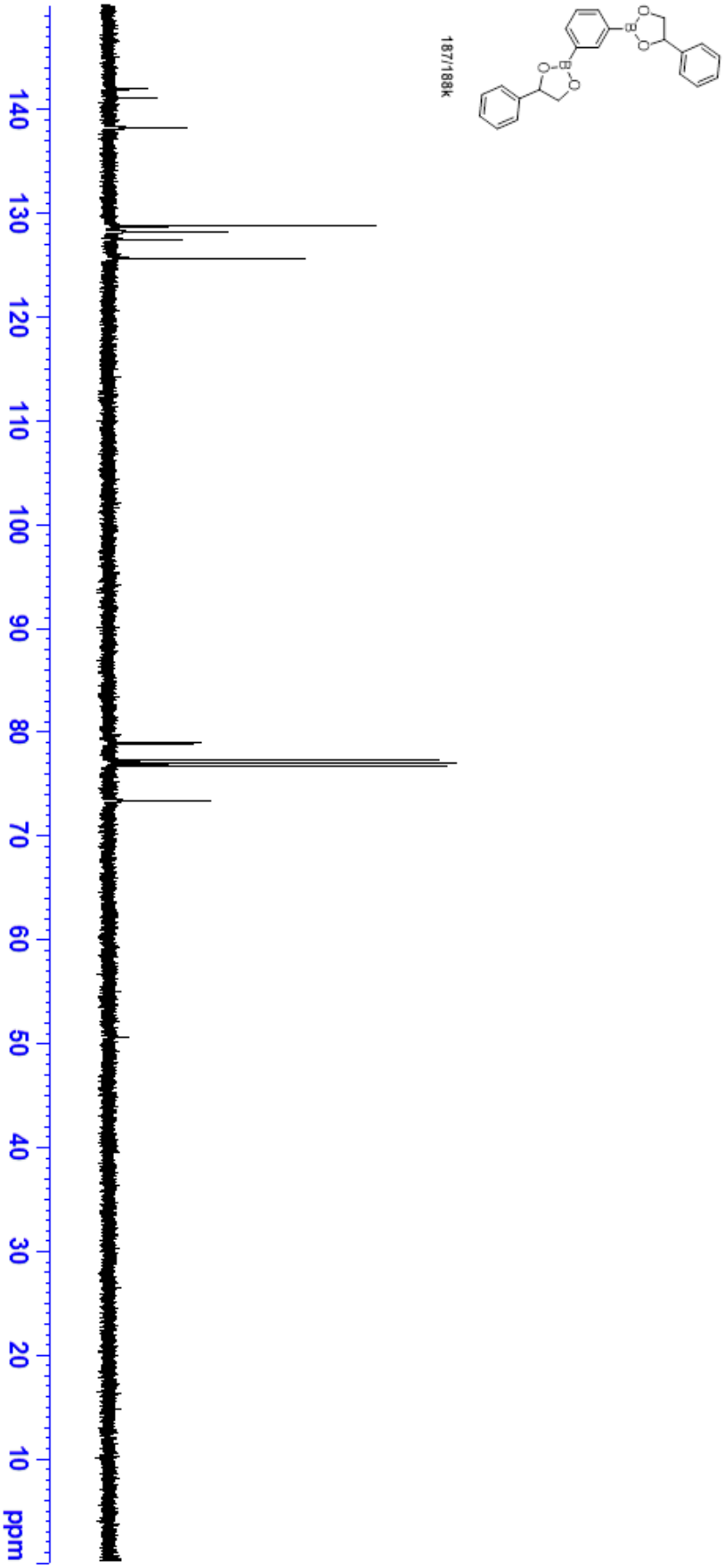



187/186j
500 MHz; $CDCl_3$
1.00
2.04
1.11
4.17
6.44
2.18
2.09
2.07
2.06
2.10
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

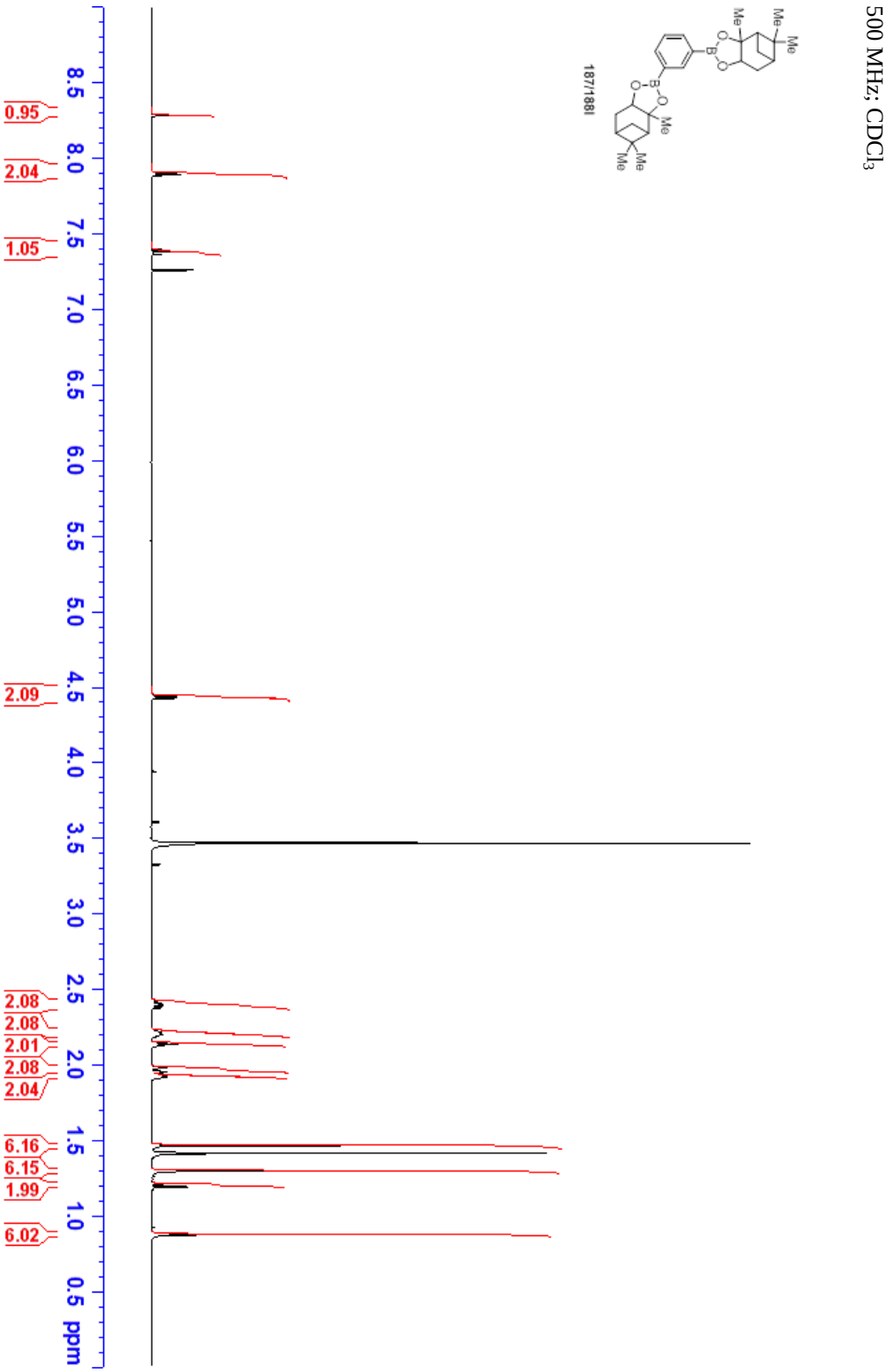

187/188J
125 MHz; $CDCl_3$
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm
138.0
137.5
137.0
ppm



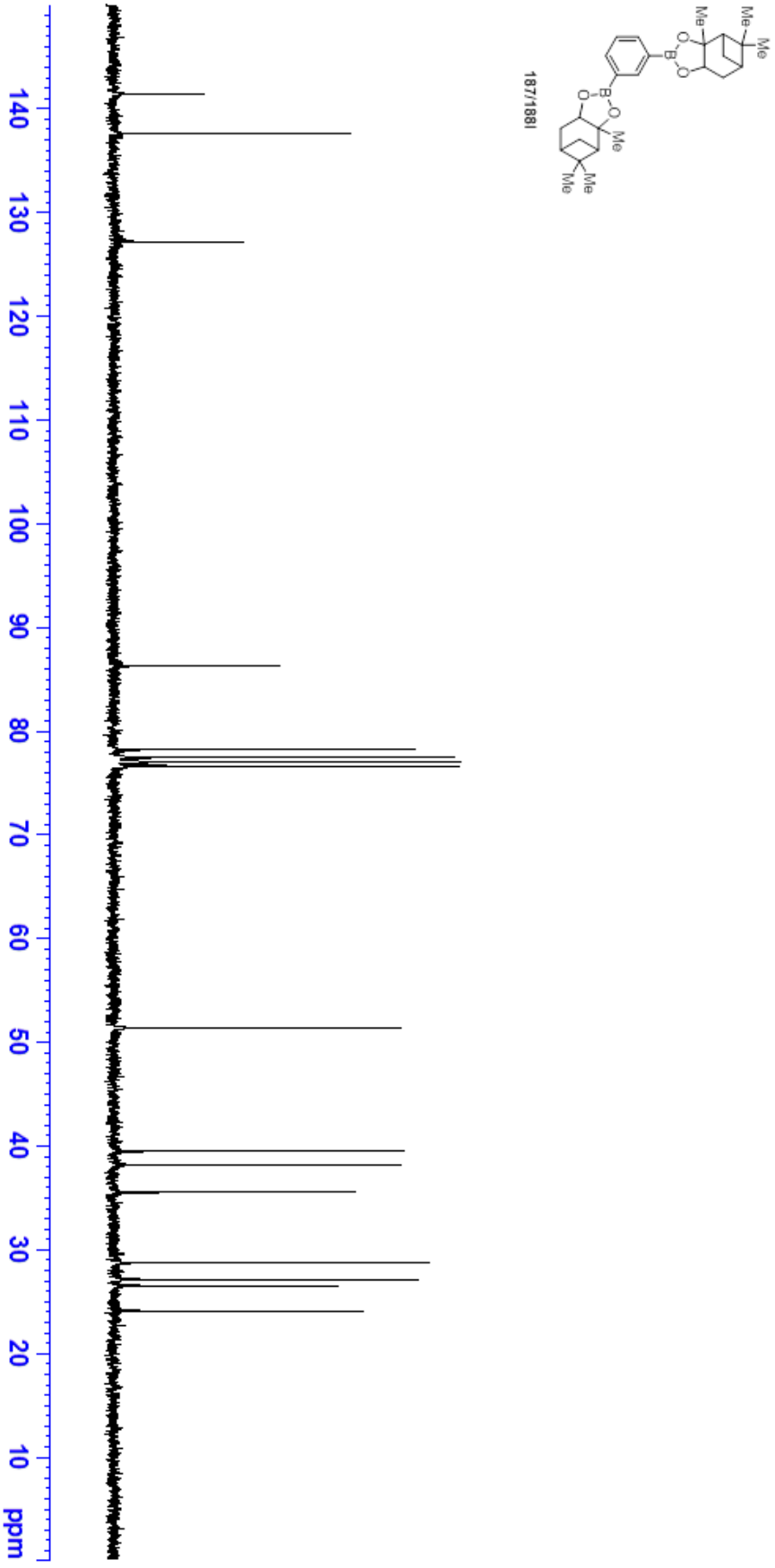
500 MHz; $CDCl_3$

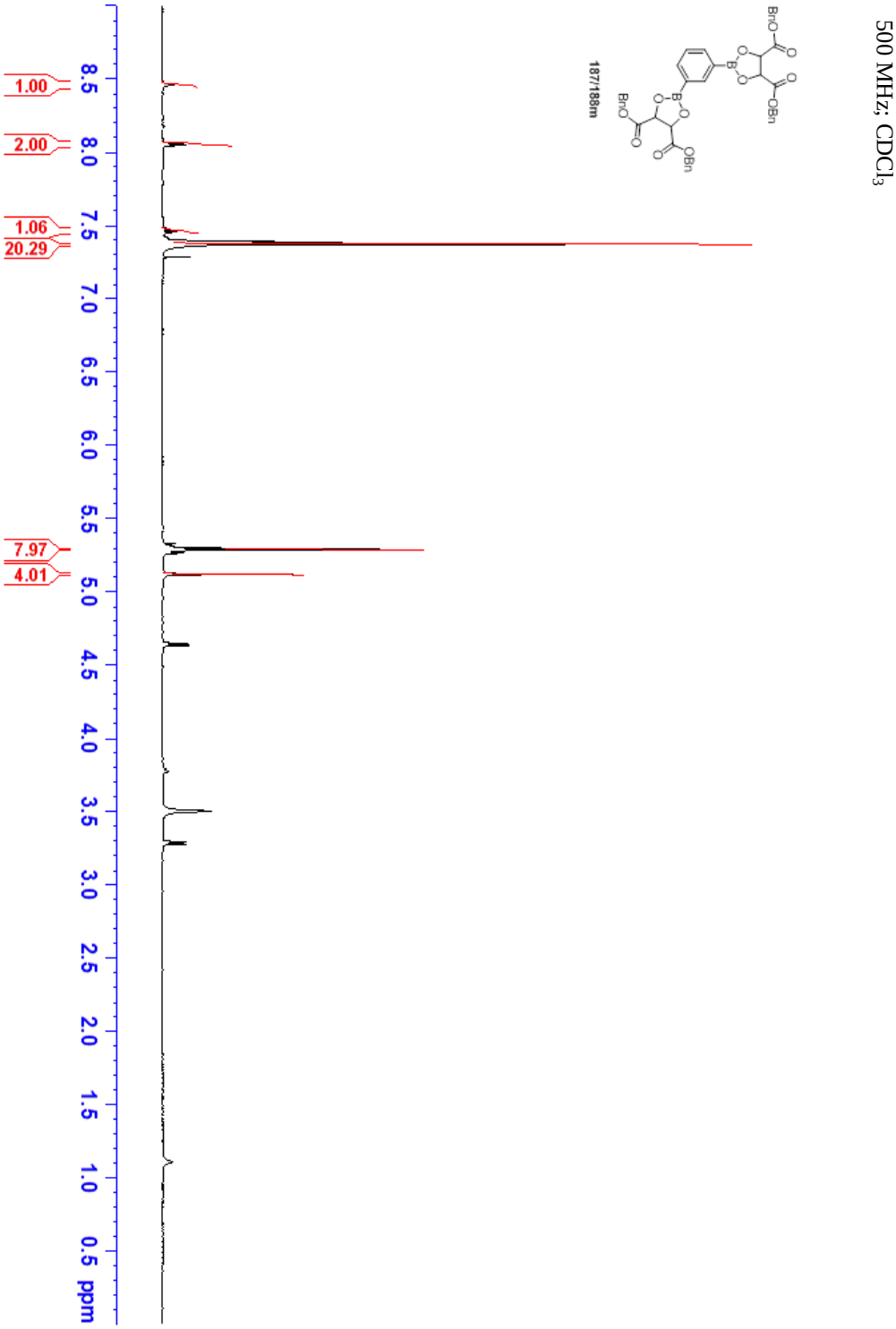


125 MHz; $CDCl_3$

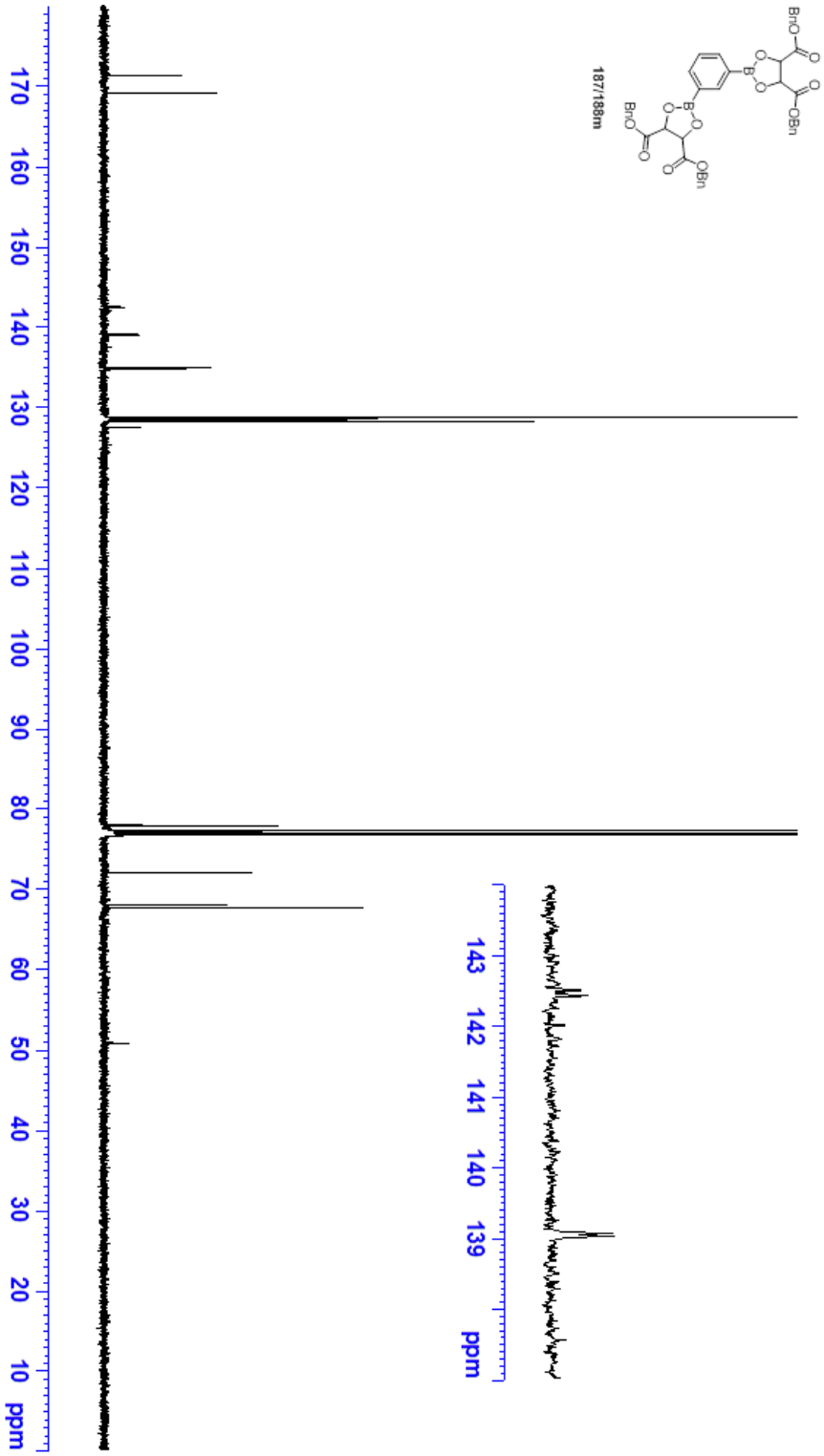

500 MHz; $CDCl_3$
187/188I
Me
Me
Me
O
B
O
B
O
O
Me
Me
Me
0.95
2.04
1.05
2.09
2.08
2.08
2.01
2.08
2.04
6.16
6.15
1.99
6.02
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

125 MHz; $CDCl_3$




500 MHz; $CDCl_3$
187/188m
1.00
2.00
1.06
20.29
7.97
4.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

125 MHz; $CDCl_3$



X-Ray Crystallographic Data

All X-ray structures were obtained by Dr. Mary Mahon at the University of Bath and deposited into the Cambridge Crystallographic Data Centre.

X-ray Crystallographic Data for (*S*,*S*)-*p*-tolyl-α-amino nitrile 122b

CCDC No. - 811794

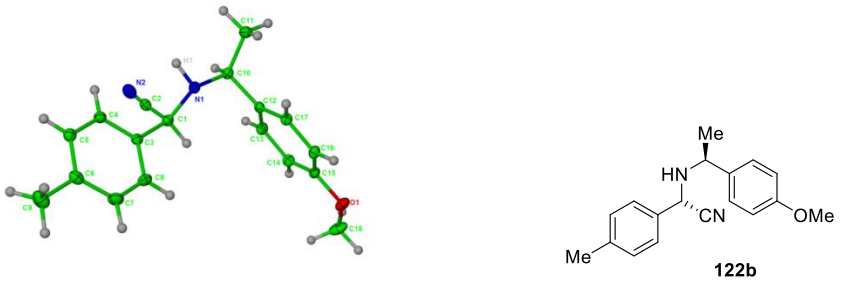


Figure 54 - X-ray crystal structure of (*S*,*S*)-*p*-tolyl-α-amino nitrile 122b

Table 1. Crystal data and structure refinement for 1.

Identification code	k10tdj1
Empirical formula	C18 H21 Cl N2 O
Formula weight	316.82
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P212121
Unit cell dimensions	a = 6.5880(1)Å α = 90°
	b = 13.1300(3)Å β = 90°
	c = 18.3980(3)Å γ = 90°
Volume	1591.43(5) $Å^3$
Z	4
Density (calculated)	1.322 Mg/m^3
Absorption coefficient	0.244 mm^{-1}

F(000)	672
Crystal size	0.40 x 0.30 x 0.10 mm
Theta range for data collection	3.63 to 27.44^{o}
Index ranges	-8<=h<=8; -17<=k<=17; -23<=l<=23
Reflections collected	30416
Independent reflections	3623 [R(int) = 0.0776]
Reflections observed (>2σ)	2751
Data Completeness	0.996
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.954 and 0.880
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3623 / 1 / 198
Goodness-of-fit on F^2	1.038
Final R indices [I>2σ(I)]	R1 = 0.0399 wR2 = 0.0855
R indices (all data)	R1 = 0.0661 wR2 = 0.0960
Absolute structure parameter	-0.7(15)
Largest diff. peak and hole	0.182 and -0.182 eÅ^{-3}

Notes:

H1 located and refined at a distance of 0.98 Å from N1.

Absolute stereochemistry not definitive from crystallography – assigned on basis of chemical information.

Hydrogen bonding present.

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
N1-H1	0.974	2.209	171.54	3.175	N2 [x-1/2, -y+3/2, -z+2]

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1.U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
O(1)	9437(2)	9398(1)	6249(1)	40(1)
N(1)	3210(2)	7996(1)	8612(1)	28(1)
N(2)	5415(2)	8228(1)	10287(1)	43(1)
C(1)	3909(2)	8867(1)	9040(1)	29(1)
C(2)	4784(3)	8532(1)	9749(1)	32(1)
C(3)	2218(3)	9635(1)	9159(1)	28(1)
C(4)	681(3)	9463(1)	9657(1)	31(1)
C(5)	-864(3)	10164(1)	9755(1)	33(1)
C(6)	-905(3)	11072(1)	9364(1)	37(1)
C(7)	626(3)	11230(1)	8856(1)	44(1)
C(8)	2170(3)	10532(1)	8758(1)	38(1)
C(9)	-2564(3)	11845(2)	9488(1)	54(1)
C(10)	4847(2)	7291(1)	8386(1)	29(1)
C(11)	3858(3)	6314(1)	8122(1)	39(1)
C(12)	6147(2)	7810(1)	7820(1)	26(1)
C(13)	8105(3)	8128(1)	7969(1)	32(1)
C(14)	9259(2)	8662(1)	7464(1)	32(1)
C(15)	8440(2)	8877(1)	6790(1)	29(1)
C(16)	6490(3)	8555(1)	6623(1)	32(1)
C(17)	5365(3)	8031(1)	7132(1)	29(1)
C(18)	11290(3)	9895(2)	6440(1)	53(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

O(1)-C(15)	1.3745(18)	O(1)-C(18)	1.428(2)
N(1)-C(1)	1.463(2)	N(1)-C(10)	1.480(2)
N(1)-H(1)	0.974(5)	N(2)-C(2)	1.145(2)
C(1)-C(2)	1.493(2)	C(1)-C(3)	1.518(2)
C(1)-H(1A)	1.0000	C(3)-C(4)	1.384(2)
C(3)-C(8)	1.391(2)	C(4)-C(5)	1.384(2)
C(4)-H(4)	0.9500	C(5)-C(6)	1.392(2)
C(5)-H(5)	0.9500	C(6)-C(7)	1.391(3)
C(6)-C(9)	1.509(3)	C(7)-C(8)	1.381(3)
C(7)-H(7)	0.9500	C(8)-H(8)	0.9500
C(9)-H(9A)	0.9800	C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800	C(10)-C(12)	1.512(2)
C(10)-C(11)	1.519(2)	C(10)-H(10)	1.0000
C(11)-H(11A)	0.9800	C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800	C(12)-C(13)	1.383(2)
C(12)-C(17)	1.397(2)	C(13)-C(14)	1.391(2)
C(13)-H(13)	0.9500	C(14)-C(15)	1.380(2)
C(14)-H(14)	0.9500	C(15)-C(16)	1.387(2)
C(16)-C(17)	1.379(2)	C(16)-H(16)	0.9500
C(17)-H(17)	0.9500	C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800	C(18)-H(18C)	0.9800
C(15)-O(1)-C(18)	117.23(14)	C(1)-N(1)-C(10)	114.23(12)
C(1)-N(1)-H(1)	107.5(10)	C(10)-N(1)-H(1)	108.2(10)
N(1)-C(1)-C(2)	111.17(12)	N(1)-C(1)-C(3)	111.47(13)
C(2)-C(1)-C(3)	110.64(12)	N(1)-C(1)-H(1A)	107.8
C(2)-C(1)-H(1A)	107.8	C(3)-C(1)-H(1A)	107.8
N(2)-C(2)-C(1)	176.66(17)	C(4)-C(3)-C(8)	118.19(16)
C(4)-C(3)-C(1)	121.64(13)	C(8)-C(3)-C(1)	120.16(15)
C(5)-C(4)-C(3)	121.07(15)	C(5)-C(4)-H(4)	119.5
C(3)-C(4)-H(4)	119.5	C(4)-C(5)-C(6)	121.06(16)
C(4)-C(5)-H(5)	119.5	C(6)-C(5)-H(5)	119.5
C(7)-C(6)-C(5)	117.50(16)	C(7)-C(6)-C(9)	121.72(16)
C(5)-C(6)-C(9)	120.78(17)	C(8)-C(7)-C(6)	121.45(15)
C(8)-C(7)-H(7)	119.3	C(6)-C(7)-H(7)	119.3
C(7)-C(8)-C(3)	120.70(17)	C(7)-C(8)-H(8)	119.7
C(3)-C(8)-H(8)	119.7	C(6)-C(9)-H(9A)	109.5
C(6)-C(9)-H(9B)	109.5	H(9A)-C(9)-H(9B)	109.5
C(6)-C(9)-H(9C)	109.5	H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5	N(1)-C(10)-C(12)	108.92(12)
N(1)-C(10)-C(11)	107.78(13)	C(12)-C(10)-C(11)	113.78(13)
N(1)-C(10)-H(10)	108.8	C(12)-C(10)-H(10)	108.8
C(11)-C(10)-H(10)	108.8	C(10)-C(11)-H(11A)	109.5
C(10)-C(11)-H(11B)	109.5	H(11A)-C(11)-H(11B)	109.5
C(10)-C(11)-H(11C)	109.5	H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5	C(13)-C(12)-C(17)	117.52(14)

C(13)-C(12)-C(10)	121.80(13)	C(17)-C(12)-C(10)	120.61(14)
C(12)-C(13)-C(14)	121.89(14)	C(12)-C(13)-H(13)	119.1
C(14)-C(13)-H(13)	119.1	C(15)-C(14)-C(13)	119.35(15)
C(15)-C(14)-H(14)	120.3	C(13)-C(14)-H(14)	120.3
O(1)-C(15)-C(14)	124.40(15)	O(1)-C(15)-C(16)	115.68(14)
C(14)-C(15)-C(16)	119.92(14)	C(17)-C(16)-C(15)	119.95(15)
C(17)-C(16)-H(16)	120.0	C(15)-C(16)-H(16)	120.0
C(16)-C(17)-C(12)	121.36(16)	C(16)-C(17)-H(17)	119.3
C(12)-C(17)-H(17)	119.3	O(1)-C(18)-H(18A)	109.5
O(1)-C(18)-H(18B)	109.5	H(18A)-C(18)-H(18B)	109.5
O(1)-C(18)-H(18C)	109.5	H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for 1. The anisotropic displacement
factor exponent takes the form: -2 gpi^2 [h^2 a^{*2} U11 + ... + 2 h k a* b* U

Atom	U11	U22	U33	U23	U13	U12
O(1)	31(1)	48(1)	42(1)	14(1)	7(1)	-2(1)
N(1)	24(1)	33(1)	28(1)	-1(1)	0(1)	-2(1)
N(2)	47(1)	43(1)	40(1)	-4(1)	-13(1)	9(1)
C(1)	28(1)	32(1)	27(1)	2(1)	-2(1)	-2(1)
C(2)	31(1)	32(1)	35(1)	-5(1)	-3(1)	2(1)
C(3)	28(1)	28(1)	27(1)	-1(1)	-4(1)	-4(1)
C(4)	35(1)	28(1)	31(1)	2(1)	-1(1)	-1(1)
C(5)	33(1)	36(1)	32(1)	-2(1)	-2(1)	-1(1)
C(6)	39(1)	34(1)	40(1)	-5(1)	-10(1)	4(1)
C(7)	54(1)	32(1)	45(1)	9(1)	-2(1)	3(1)
C(8)	42(1)	35(1)	37(1)	9(1)	2(1)	-4(1)
C(9)	56(1)	47(1)	58(1)	-5(1)	-9(1)	17(1)
C(10)	26(1)	32(1)	29(1)	4(1)	0(1)	3(1)
C(11)	42(1)	31(1)	45(1)	1(1)	8(1)	-2(1)
C(12)	25(1)	26(1)	27(1)	-1(1)	0(1)	4(1)
C(13)	30(1)	39(1)	28(1)	2(1)	-4(1)	2(1)
C(14)	23(1)	36(1)	35(1)	0(1)	-2(1)	-1(1)
C(15)	27(1)	29(1)	31(1)	3(1)	8(1)	4(1)
C(16)	29(1)	39(1)	26(1)	3(1)	-1(1)	3(1)
C(17)	25(1)	34(1)	30(1)	-1(1)	-2(1)	-1(1)
C(18)	28(1)	59(1)	73(1)	30(1)	2(1)	-4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

Atom	x	y	z	U(eq)
H(1A)	5011	9213	8759	35
H(4)	686	8854	9936	37
H(5)	-1914	10024	10095	40
H(7)	608	11832	8569	52
H(8)	3209	10666	8413	46
H(9A)	-3779	11644	9216	80
H(9B)	-2106	12515	9320	80
H(9C)	-2884	11878	10008	80
H(10)	5709	7132	8819	35
H(11A)	2929	6469	7721	59
H(11B)	3099	6001	8522	59
H(11C)	4909	5842	7953	59
H(13)	8678	7977	8431	39
H(14)	10597	8876	7581	38
H(16)	5931	8696	6158	38
H(17)	4029	7815	7012	35
H(18A)	12287	9385	6596	79
H(18B)	11039	10375	6838	79
H(18C)	11816	10265	6018	79
H(1)	2250(20)	7617(11)	8910(8)	42(5)

Table 6. Dihedral angles [°] for 1.

Atom1 - Atom2 - Atom3 - Atom4	Dihedral
C(10) - N(1) - C(1) - C(2)	-64.30(16)
C(10) - N(1) - C(1) - C(3)	171.75(12)
N(1) - C(1) - C(2) - N(2)	-13(3)
C(3) - C(1) - C(2) - N(2)	112(3)
N(1) - C(1) - C(3) - C(4)	75.86(18)
C(2) - C(1) - C(3) - C(4)	-48.39(19)
N(1) - C(1) - C(3) - C(8)	-103.35(16)
C(2) - C(1) - C(3) - C(8)	132.40(16)
C(8) - C(3) - C(4) - C(5)	-0.1(2)
C(1) - C(3) - C(4) - C(5)	-179.29(14)
C(3) - C(4) - C(5) - C(6)	-1.0(2)
C(4) - C(5) - C(6) - C(7)	2.1(2)
C(4) - C(5) - C(6) - C(9)	-178.38(16)
C(5) - C(6) - C(7) - C(8)	-2.2(3)
C(9) - C(6) - C(7) - C(8)	178.28(17)
C(6) - C(7) - C(8) - C(3)	1.2(3)
C(4) - C(3) - C(8) - C(7)	0.0(2)
C(1) - C(3) - C(8) - C(7)	179.20(15)
C(1) - N(1) - C(10) - C(12)	-70.16(15)
C(1) - N(1) - C(10) - C(11)	165.96(12)
N(1) - C(10) - C(12) - C(13)	109.16(16)
C(11) - C(10) - C(12) - C(13)	-130.59(16)
N(1) - C(10) - C(12) - C(17)	-67.64(18)
C(11) - C(10) - C(12) - C(17)	52.6(2)
C(17) - C(12) - C(13) - C(14)	1.0(2)
C(10) - C(12) - C(13) - C(14)	-175.91(15)
C(12) - C(13) - C(14) - C(15)	-0.5(2)
C(18) - O(1) - C(15) - C(14)	-11.1(2)
C(18) - O(1) - C(15) - C(16)	169.29(15)
C(13) - C(14) - C(15) - O(1)	-179.99(15)
C(13) - C(14) - C(15) - C(16)	-0.4(2)
O(1) - C(15) - C(16) - C(17)	-179.67(15)
C(14) - C(15) - C(16) - C(17)	0.7(2)
C(15) - C(16) - C(17) - C(12)	-0.2(2)
C(13) - C(12) - C(17) - C(16)	-0.7(2)
C(10) - C(12) - C(17) - C(16)	176.27(14)

Symmetry transformations used to generate equivalent atoms:

X-ray Crystallographic Data for nitrono-boronate ester (*S*,*R*)-139d

CCDC No. - 1415709

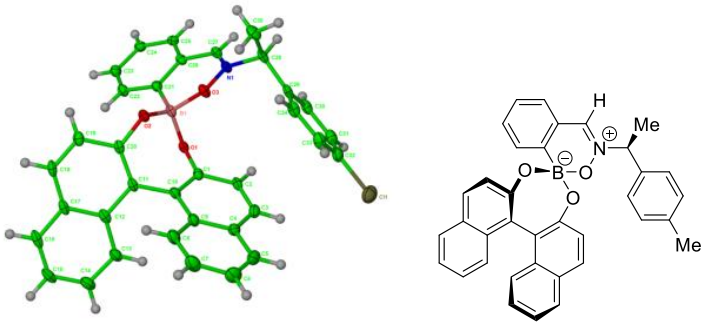


Figure 55 – X-ray crystal structure of nitrono-boronate ester (*S*,*R*)-139d

Table 1. Crystal data and structure refinement for 1.

Identification code	k12tdj2
Empirical formula	C36.50 H26.50 B Cl5.50 N O3
Formula weight	732.87
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Hexagonal
Space group	P65
Unit cell dimensions	a = 22.2610(3)Å alpha = 90°
	b = 22.2610(3)Å beta = 90°
	c = 14.8460(2)Å gamma = 120°
Volume	6371.32(15) $Å^3$
Z	6
Density (calculated)	1.146 Mg/m^3
Absorption coefficient	0.404 mm^{-1}
F(000)	2250
Crystal size	0.45 x 0.30 x 0.30 mm
Theta range for data collection	3.66 to 27.48°
Index ranges	-24<=h<=0; 0<=k<=28; -18<=l<=19
Reflections collected	9679

Independent reflections	9679 [R(int) = 0.0000]
Reflections observed (>2sigma)	7174
Data Completeness	0.997
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.955 and 0.828
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9679 / 31 / 434
Goodness-of-fit on F^2	1.038
Final R indices [I>2sigma(I)]	R1 = 0.0655 *wR*2 = 0.1675
R indices (all data)	R1 = 0.0910 *wR*2 = 0.1793
Absolute structure parameter	0.09(7)
Largest diff. peak and hole	0.306 and -0.287 eÅ^{-3}

Notes:

The asymmetric unit in this structure contains one molecule of compound X, one full molecule of chloroform in which the chlorides have been modelled as being are disordered over 2 positions and a diffuse region of solvent for which a sensible model could not be constructed. Thus the latter was treated with PLATON-SQUEEZE, and based on pre-PLATON analysis of the difference Fourier electron density map, it has been included herein as one half of a chloroform molecule per asymmetric unit.

Some distance and ADP restraints were included in the full molecule of chloroform – in order to assist convergence.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1.U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
Cl(1)	1462(1)	7799(1)	359(1)	71(1)
Cl(2)	6207(3)	8096(4)	-469(4)	129(2)
Cl(3)	7066(2)	7627(3)	355(5)	146(2)
Cl(4)	6367(3)	8171(4)	1426(5)	103(2)
Cl(2A)	6504(4)	7974(3)	-551(3)	148(2)
Cl(3A)	6951(3)	7391(3)	816(4)	127(2)
Cl(4A)	6434(6)	8296(6)	1292(7)	170(5)
O(1)	2048(1)	6304(1)	4084(1)	34(1)
O(2)	1247(1)	5052(1)	4199(1)	36(1)
O(3)	1815(1)	5474(1)	2856(1)	39(1)
N(1)	2370(1)	5638(1)	2329(2)	34(1)
C(1)	1546(1)	6458(1)	3850(2)	34(1)
C(2)	1714(2)	6977(2)	3186(2)	40(1)
C(3)	1248(2)	7157(2)	2925(2)	45(1)
C(4)	562(2)	6796(2)	3262(2)	44(1)
C(5)	33(2)	6928(2)	2922(2)	60(1)
C(6)	-636(2)	6548(2)	3222(3)	67(1)
C(7)	-813(2)	6013(2)	3842(3)	63(1)
C(8)	-323(2)	5883(2)	4189(2)	51(1)
C(9)	378(2)	6269(2)	3928(2)	41(1)
C(10)	908(1)	6140(2)	4271(2)	36(1)
C(11)	785(1)	5659(2)	5032(2)	35(1)
C(12)	513(1)	5742(2)	5883(2)	40(1)
C(13)	438(2)	6323(2)	6079(2)	46(1)
C(14)	179(2)	6371(2)	6903(2)	57(1)
C(15)	-20(2)	5864(2)	7547(2)	55(1)
C(16)	64(2)	5317(2)	7404(2)	51(1)
C(17)	346(1)	5230(2)	6577(2)	40(1)
C(18)	493(2)	4699(2)	6442(2)	44(1)
C(19)	805(1)	4653(2)	5673(2)	40(1)
C(20)	956(1)	5142(2)	4967(2)	36(1)
C(21)	2591(1)	5579(1)	4200(2)	34(1)
C(22)	2737(2)	5497(2)	5092(2)	39(1)
C(23)	3362(2)	5545(2)	5327(2)	41(1)
C(24)	3859(2)	5663(2)	4680(2)	40(1)
C(25)	3726(2)	5730(2)	3789(2)	38(1)
C(26)	3099(1)	5682(1)	3557(2)	34(1)
C(27)	2956(1)	5738(2)	2619(2)	36(1)
C(28)	2210(2)	5631(2)	1353(2)	42(1)
C(29)	2008(2)	6172(2)	1140(2)	40(1)
C(30)	2521(2)	6866(2)	1103(2)	44(1)
C(31)	2363(2)	7372(2)	860(2)	49(1)
C(32)	1680(2)	7174(2)	666(2)	50(1)
C(33)	1162(2)	6495(2)	706(2)	51(1)

C(34)	1322(2)	5992(2)	959(2)	47(1)
C(35)	1682(2)	4897(2)	1088(2)	52(1)
C(36)	6335(2)	7682(2)	513(3)	86(1)
B(1)	1916(2)	5603(2)	3871(2)	35(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

Cl(1)-C(32)	1.747(3)	Cl(2)-C(36)	1.821(8)
Cl(3)-C(36)	1.709(6)	Cl(4)-C(36)	1.718(6)
Cl(2A)-C(36)	1.677(7)	Cl(3A)-C(36)	1.844(7)
Cl(4A)-C(36)	1.718	O(1)-C(1)	1.368(3)
O(1)-B(1)	1.471(4)	O(2)-C(20)	1.374(3)
O(2)-B(1)	1.462(4)	O(3)-N(1)	1.349(3)
O(3)-B(1)	1.530(4)	N(1)-C(27)	1.284(4)
N(1)-C(28)	1.491(4)	C(1)-C(10)	1.380(4)
C(1)-C(2)	1.419(4)	C(2)-C(3)	1.342(4)
C(3)-C(4)	1.416(5)	C(4)-C(9)	1.429(4)
C(4)-C(5)	1.440(5)	C(5)-C(6)	1.368(6)
C(6)-C(7)	1.397(6)	C(7)-C(8)	1.362(5)
C(8)-C(9)	1.408(5)	C(9)-C(10)	1.440(4)
C(10)-C(11)	1.484(4)	C(11)-C(20)	1.383(4)
C(11)-C(12)	1.453(4)	C(12)-C(13)	1.415(5)
C(12)-C(17)	1.440(4)	C(13)-C(14)	1.379(5)
C(14)-C(15)	1.373(6)	C(15)-C(16)	1.337(6)
C(16)-C(17)	1.436(4)	C(17)-C(18)	1.390(5)
C(18)-C(19)	1.366(4)	C(19)-C(20)	1.425(4)
C(21)-C(22)	1.396(4)	C(21)-C(26)	1.409(4)
C(21)-B(1)	1.604(4)	C(22)-C(23)	1.387(4)
C(23)-C(24)	1.388(4)	C(24)-C(25)	1.379(4)
C(25)-C(26)	1.389(4)	C(26)-C(27)	1.447(4)
C(28)-C(35)	1.511(5)	C(28)-C(29)	1.513(5)
C(29)-C(30)	1.389(5)	C(29)-C(34)	1.399(4)
C(30)-C(31)	1.384(5)	C(31)-C(32)	1.387(5)
C(32)-C(33)	1.369(5)	C(33)-C(34)	1.384(5)
C(1)-O(1)-B(1)	117.2(2)	C(20)-O(2)-B(1)	120.8(2)
N(1)-O(3)-B(1)	119.4(2)	C(27)-N(1)-O(3)	124.4(2)
C(27)-N(1)-C(28)	123.1(2)	O(3)-N(1)-C(28)	112.3(2)
O(1)-C(1)-C(10)	121.1(2)	O(1)-C(1)-C(2)	117.7(2)
C(10)-C(1)-C(2)	121.2(3)	C(3)-C(2)-C(1)	121.0(3)
C(2)-C(3)-C(4)	120.3(3)	C(3)-C(4)-C(9)	119.6(3)
C(3)-C(4)-C(5)	121.4(3)	C(9)-C(4)-C(5)	118.9(3)
C(6)-C(5)-C(4)	120.5(3)	C(5)-C(6)-C(7)	119.9(3)
C(8)-C(7)-C(6)	121.1(4)	C(7)-C(8)-C(9)	121.8(3)
C(8)-C(9)-C(4)	117.8(3)	C(8)-C(9)-C(10)	123.3(3)
C(4)-C(9)-C(10)	118.9(3)	C(1)-C(10)-C(9)	118.2(3)
C(1)-C(10)-C(11)	119.1(2)	C(9)-C(10)-C(11)	122.6(2)
C(20)-C(11)-C(12)	118.1(2)	C(20)-C(11)-C(10)	121.3(2)
C(12)-C(11)-C(10)	120.6(3)	C(13)-C(12)-C(17)	118.4(3)
C(13)-C(12)-C(11)	122.8(3)	C(17)-C(12)-C(11)	118.7(3)
C(14)-C(13)-C(12)	119.8(3)	C(15)-C(14)-C(13)	122.0(4)
C(16)-C(15)-C(14)	120.2(3)	C(15)-C(16)-C(17)	121.9(3)
C(18)-C(17)-C(16)	122.9(3)	C(18)-C(17)-C(12)	119.5(3)
C(16)-C(17)-C(12)	117.5(3)	C(19)-C(18)-C(17)	121.9(3)
C(18)-C(19)-C(20)	119.5(3)	O(2)-C(20)-C(11)	121.6(2)
O(2)-C(20)-C(19)	116.5(3)	C(11)-C(20)-C(19)	121.8(3)

C(22)-C(21)-C(26)	116.3(3)	C(22)-C(21)-B(1)	125.2(2)
C(26)-C(21)-B(1)	118.5(2)	C(23)-C(22)-C(21)	121.3(3)
C(22)-C(23)-C(24)	120.9(3)	C(25)-C(24)-C(23)	119.4(3)
C(24)-C(25)-C(26)	119.4(3)	C(25)-C(26)-C(21)	122.6(2)
C(25)-C(26)-C(27)	119.1(2)	C(21)-C(26)-C(27)	118.3(2)
N(1)-C(27)-C(26)	123.8(2)	N(1)-C(28)-C(35)	108.5(2)
N(1)-C(28)-C(29)	111.0(2)	C(35)-C(28)-C(29)	115.2(3)
C(30)-C(29)-C(34)	118.8(3)	C(30)-C(29)-C(28)	119.2(3)
C(34)-C(29)-C(28)	121.9(3)	C(31)-C(30)-C(29)	120.9(3)
C(30)-C(31)-C(32)	118.7(3)	C(33)-C(32)-C(31)	121.7(3)
C(33)-C(32)-Cl(1)	118.4(3)	C(31)-C(32)-Cl(1)	119.9(3)
C(32)-C(33)-C(34)	119.3(3)	C(33)-C(34)-C(29)	120.5(3)
Cl(2A)-C(36)-Cl(3)	82.0(4)	Cl(2A)-C(36)-Cl(4A)	114.2(6)
Cl(3)-C(36)-Cl(4A)	113.6(5)	Cl(2A)-C(36)-Cl(4)	124.6(5)
Cl(3)-C(36)-Cl(4)	114.4(4)	Cl(4A)-C(36)-Cl(4)	10.4(7)
Cl(2A)-C(36)-Cl(2)	27.4(3)	Cl(3)-C(36)-Cl(2)	108.8(4)
Cl(4A)-C(36)-Cl(2)	97.3(6)	Cl(4)-C(36)-Cl(2)	106.2(4)
Cl(2A)-C(36)-Cl(3A)	107.7(4)	Cl(3)-C(36)-Cl(3A)	26.4(3)
Cl(4A)-C(36)-Cl(3A)	107.0(5)	Cl(4)-C(36)-Cl(3A)	103.2(4)
Cl(2)-C(36)-Cl(3A)	134.9(3)	O(2)-B(1)-O(1)	113.4(2)
O(2)-B(1)-O(3)	100.3(2)	O(1)-B(1)-O(3)	110.1(2)
O(2)-B(1)-C(21)	116.7(2)	O(1)-B(1)-C(21)	106.0(2)
O(3)-B(1)-C(21)	110.3(2)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for 1. The anisotropic displacement
factor exponent takes the form: -2 gpi^2 [h^2 a^{*2} U11 + ... + 2 h k a* b* U

Atom	U11	U22	U33	U23	U13	U12
Cl(1)	84(1)	70(1)	63(1)	2(1)	-16(1)	42(1)
Cl(2)	111(3)	118(4)	115(3)	5(2)	26(2)	25(2)
Cl(3)	78(2)	152(4)	198(6)	-107(4)	-18(3)	50(3)
Cl(4)	70(2)	91(2)	108(3)	-48(2)	25(2)	11(2)
Cl(2A)	196(7)	113(3)	71(2)	3(2)	12(3)	29(4)
Cl(3A)	73(2)	150(4)	134(4)	-3(3)	1(2)	36(2)
Cl(4A)	172(8)	172(8)	127(5)	-40(5)	44(4)	58(6)
O(1)	31(1)	39(1)	26(1)	1(1)	2(1)	14(1)
O(2)	36(1)	39(1)	27(1)	-1(1)	2(1)	16(1)
O(3)	29(1)	54(1)	28(1)	-3(1)	2(1)	16(1)
N(1)	34(1)	41(1)	25(1)	-3(1)	2(1)	16(1)
C(1)	38(1)	37(1)	25(1)	-2(1)	-3(1)	17(1)
C(2)	43(2)	43(2)	27(1)	3(1)	6(1)	17(1)
C(3)	60(2)	43(2)	34(2)	4(1)	1(1)	26(2)
C(4)	57(2)	55(2)	33(1)	0(1)	-1(1)	36(2)
C(5)	80(3)	83(3)	42(2)	8(2)	-5(2)	60(2)
C(6)	63(2)	104(3)	59(2)	3(2)	-8(2)	61(2)
C(7)	50(2)	100(3)	49(2)	4(2)	2(2)	46(2)
C(8)	51(2)	77(2)	34(2)	5(2)	2(1)	38(2)
C(9)	45(2)	54(2)	28(1)	2(1)	1(1)	28(1)
C(10)	38(1)	48(2)	25(1)	-2(1)	1(1)	23(1)
C(11)	26(1)	48(2)	25(1)	3(1)	1(1)	14(1)
C(12)	26(1)	63(2)	28(1)	-2(1)	-2(1)	19(1)
C(13)	48(2)	66(2)	31(2)	-3(1)	1(1)	34(2)
C(14)	60(2)	83(2)	40(2)	-7(2)	5(2)	46(2)
C(15)	46(2)	90(3)	32(2)	-7(2)	6(1)	37(2)
C(16)	28(1)	78(2)	26(1)	7(1)	2(1)	11(2)
C(17)	26(1)	55(2)	25(1)	4(1)	1(1)	11(1)
C(18)	35(1)	52(2)	29(1)	14(1)	5(1)	9(1)
C(19)	32(1)	42(2)	36(1)	5(1)	-1(1)	10(1)
C(20)	28(1)	44(2)	27(1)	3(1)	0(1)	12(1)
C(21)	38(1)	35(1)	30(1)	-3(1)	-2(1)	17(1)
C(22)	40(2)	49(2)	29(1)	-2(1)	-1(1)	22(1)
C(23)	47(2)	50(2)	31(1)	-1(1)	-4(1)	27(1)
C(24)	44(2)	45(2)	39(2)	-3(1)	-4(1)	28(1)
C(25)	43(2)	39(2)	39(2)	-3(1)	2(1)	24(1)
C(26)	34(1)	33(1)	30(1)	-6(1)	0(1)	14(1)
C(27)	36(1)	40(2)	28(1)	-4(1)	1(1)	17(1)
C(28)	38(2)	59(2)	21(1)	-3(1)	4(1)	18(1)
C(29)	35(1)	54(2)	19(1)	0(1)	1(1)	15(1)
C(30)	36(2)	59(2)	27(1)	-2(1)	-2(1)	16(1)
C(31)	43(2)	49(2)	34(2)	-1(1)	0(1)	8(1)
C(32)	58(2)	62(2)	32(2)	6(1)	-1(1)	31(2)
C(33)	37(2)	67(2)	39(2)	6(1)	-1(1)	18(2)
C(34)	33(2)	55(2)	35(1)	2(1)	-1(1)	10(1)

C(35)	54(2)	62(2)	34(2)	-16(1)	-5(1)	25(2)
C(36)	73(3)	77(3)	81(3)	-13(2)	17(2)	17(2)
B(1)	35(2)	40(2)	26(1)	-1(1)	3(1)	15(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

Atom	x	y	z	U(eq)
H(2)	2162	7199	2921	48
H(3)	1380	7529	2513	54
H(5)	149	7282	2485	72
H(6)	-979	6648	3010	80
H(7)	-1283	5736	4025	75
H(8)	-457	5522	4619	61
H(13)	566	6679	5643	55
H(14)	137	6767	7029	68
H(15)	-218	5901	8096	65
H(16)	-67	4977	7863	61
H(18)	374	4358	6898	53
H(19)	920	4298	5609	48
H(22)	2401	5406	5546	47
H(23)	3452	5497	5941	49
H(24)	4287	5698	4848	48
H(25)	4060	5808	3338	46
H(27)	3317	5855	2194	43
H(28)	2645	5760	1012	51
H(30)	2986	6995	1245	53
H(31)	2717	7845	828	59
H(33)	698	6370	562	61
H(34)	963	5523	1010	56
H(35A)	1244	4756	1403	78
H(35B)	1855	4585	1253	78
H(35C)	1604	4875	436	78
H(36)	5927	7204	578	103

Table 6. Dihedral angles [°] for 1.

Atom1 - Atom2 - Atom3 - Atom4	Dihedral
B(1) - O(3) - N(1) - C(27)	18.0(4)
B(1) - O(3) - N(1) - C(28)	-167.1(2)
B(1) - O(1) - C(1) - C(10)	67.5(3)
B(1) - O(1) - C(1) - C(2)	-114.9(3)
O(1) - C(1) - C(2) - C(3)	-179.7(3)
C(10) - C(1) - C(2) - C(3)	-2.2(4)
C(1) - C(2) - C(3) - C(4)	-4.7(5)
C(2) - C(3) - C(4) - C(9)	4.2(5)
C(2) - C(3) - C(4) - C(5)	-173.2(3)
C(3) - C(4) - C(5) - C(6)	176.5(4)
C(9) - C(4) - C(5) - C(6)	-0.9(5)
C(4) - C(5) - C(6) - C(7)	-2.1(6)
C(5) - C(6) - C(7) - C(8)	3.2(6)
C(6) - C(7) - C(8) - C(9)	-1.3(6)
C(7) - C(8) - C(9) - C(4)	-1.6(5)
C(7) - C(8) - C(9) - C(10)	-179.2(3)
C(3) - C(4) - C(9) - C(8)	-174.8(3)
C(5) - C(4) - C(9) - C(8)	2.6(4)
C(3) - C(4) - C(9) - C(10)	2.9(4)
C(5) - C(4) - C(9) - C(10)	-179.7(3)
O(1) - C(1) - C(10) - C(9)	-173.3(2)
C(2) - C(1) - C(10) - C(9)	9.2(4)
O(1) - C(1) - C(10) - C(11)	4.2(4)
C(2) - C(1) - C(10) - C(11)	-173.3(2)
C(8) - C(9) - C(10) - C(1)	168.1(3)
C(4) - C(9) - C(10) - C(1)	-9.4(4)
C(8) - C(9) - C(10) - C(11)	-9.3(4)
C(4) - C(9) - C(10) - C(11)	173.1(3)
C(1) - C(10) - C(11) - C(20)	-48.2(4)
C(9) - C(10) - C(11) - C(20)	129.2(3)
C(1) - C(10) - C(11) - C(12)	128.5(3)
C(9) - C(10) - C(11) - C(12)	-54.0(4)
C(20) - C(11) - C(12) - C(13)	168.4(3)
C(10) - C(11) - C(12) - C(13)	-8.5(4)
C(20) - C(11) - C(12) - C(17)	-8.3(4)
C(10) - C(11) - C(12) - C(17)	174.9(2)
C(17) - C(12) - C(13) - C(14)	-3.0(4)
C(11) - C(12) - C(13) - C(14)	-179.7(3)
C(12) - C(13) - C(14) - C(15)	-0.9(5)
C(13) - C(14) - C(15) - C(16)	3.2(5)
C(14) - C(15) - C(16) - C(17)	-1.4(5)
C(15) - C(16) - C(17) - C(18)	174.3(3)
C(15) - C(16) - C(17) - C(12)	-2.5(4)
C(13) - C(12) - C(17) - C(18)	-172.3(3)
C(11) - C(12) - C(17) - C(18)	4.5(4)
C(13) - C(12) - C(17) - C(16)	4.6(4)

C(11) - C(12) - C(17) - C(16)	-178.6(2)
C(16) - C(17) - C(18) - C(19)	-175.5(3)
C(12) - C(17) - C(18) - C(19)	1.2(4)
C(17) - C(18) - C(19) - C(20)	-3.0(4)
B(1) - O(2) - C(20) - C(11)	61.2(3)
B(1) - O(2) - C(20) - C(19)	-122.2(3)
C(12) - C(11) - C(20) - O(2)	-176.8(2)
C(10) - C(11) - C(20) - O(2)	0.0(4)
C(12) - C(11) - C(20) - C(19)	6.7(4)
C(10) - C(11) - C(20) - C(19)	-176.5(2)
C(18) - C(19) - C(20) - O(2)	-177.7(2)
C(18) - C(19) - C(20) - C(11)	-1.1(4)
C(26) - C(21) - C(22) - C(23)	2.8(4)
B(1) - C(21) - C(22) - C(23)	-174.1(3)
C(21) - C(22) - C(23) - C(24)	-1.4(5)
C(22) - C(23) - C(24) - C(25)	-0.3(4)
C(23) - C(24) - C(25) - C(26)	0.4(4)
C(24) - C(25) - C(26) - C(21)	1.2(4)
C(24) - C(25) - C(26) - C(27)	-178.7(3)
C(22) - C(21) - C(26) - C(25)	-2.7(4)
B(1) - C(21) - C(26) - C(25)	174.3(3)
C(22) - C(21) - C(26) - C(27)	177.2(3)
B(1) - C(21) - C(26) - C(27)	-5.7(4)
O(3) - N(1) - C(27) - C(26)	0.4(4)
C(28) - N(1) - C(27) - C(26)	-174.0(3)
C(25) - C(26) - C(27) - N(1)	173.5(3)
C(21) - C(26) - C(27) - N(1)	-6.5(4)
C(27) - N(1) - C(28) - C(35)	110.2(3)
O(3) - N(1) - C(28) - C(35)	-64.8(3)
C(27) - N(1) - C(28) - C(29)	-122.2(3)
O(3) - N(1) - C(28) - C(29)	62.8(3)
N(1) - C(28) - C(29) - C(30)	75.3(3)
C(35) - C(28) - C(29) - C(30)	-160.9(3)
N(1) - C(28) - C(29) - C(34)	-106.3(3)
C(35) - C(28) - C(29) - C(34)	17.5(4)
C(34) - C(29) - C(30) - C(31)	-2.2(4)
C(28) - C(29) - C(30) - C(31)	176.3(3)
C(29) - C(30) - C(31) - C(32)	0.8(4)
C(30) - C(31) - C(32) - C(33)	-0.1(5)
C(30) - C(31) - C(32) - Cl(1)	179.9(2)
C(31) - C(32) - C(33) - C(34)	0.9(5)
Cl(1) - C(32) - C(33) - C(34)	-179.2(3)
C(32) - C(33) - C(34) - C(29)	-2.3(5)
C(30) - C(29) - C(34) - C(33)	2.9(4)
C(28) - C(29) - C(34) - C(33)	-175.5(3)
C(20) - O(2) - B(1) - O(1)	-30.8(3)
C(20) - O(2) - B(1) - O(3)	-148.1(2)
C(20) - O(2) - B(1) - C(21)	92.9(3)
C(1) - O(1) - B(1) - O(2)	-51.8(3)
C(1) - O(1) - B(1) - O(3)	59.6(3)
C(1) - O(1) - B(1) - C(21)	178.9(2)
N(1) - O(3) - B(1) - O(2)	-150.4(2)
N(1) - O(3) - B(1) - O(1)	89.9(3)

N(1) - O(3) - B(1) - C(21)	-26.7(3)
C(22) - C(21) - B(1) - O(2)	-49.1(4)
C(26) - C(21) - B(1) - O(2)	134.2(3)
C(22) - C(21) - B(1) - O(1)	78.3(3)
C(26) - C(21) - B(1) - O(1)	-98.5(3)
C(22) - C(21) - B(1) - O(3)	-162.5(3)
C(26) - C(21) - B(1) - O(3)	20.7(3)

Symmetry transformations used to generate equivalent atoms:

7 References

(1) Knowles, W. S. *Accounts Chem. Res.* **1983**, *16*, 106.
(2) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *Journal of the American Chemical Society* **1988**, *110*, 1968.
(3) Noyori, R. *Advanced Synthesis & Catalysis* **2003**, *345*, 15.
(4) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *Journal of the American Chemical Society* **2000**, *122*, 4243.
(5) List, B.; Lerner, R. A.; Barbas, C. F. *Journal of the American Chemical Society* **2000**, *122*, 2395.
(6) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *Journal of the American Chemical Society* **2005**, *127*, 32.
(7) Evans, D. A.; Bartroli, J.; Shih, T. L. *Journal of the American Chemical Society* **1981**, *103*, 2127.
(8) Corey, E. J.; Enders, D. *Tetrahedron Letters* **1976**, 3.
(9) Svedendahl, M.; Hult, K.; Berglund, P. *Journal of the American Chemical Society* **2005**, *127*, 17988.
(10) Fryzuk, M. D.; Bosnich, B. *Journal of the American Chemical Society* **1977**, *99*, 6262.
(11) Fabro, S.; Smith, R. L.; Williams, R. T. *Nature* **1967**, *215*, 296.
(12) Kumar, A. P.; Jin, D.; Lee, Y. I. *Appl. Spectrosc. Rev.* **2009**, *44*, 267.
(13) Cahn, R. S.; Ingold, C.; Prelog, V. *Angewandte Chemie-International Edition* **1966**, *5*, 385.
(14) Perez-Fuertes, Y.; Taylor, J. E.; Tickell, D. A.; Mahon, M. F.; Bull, S. D.; James, T. D. *Journal of Organic Chemistry* **2011**, *76*, 6038.
(15) Leung, D.; Kang, S. O.; Anslyn, E. V. *Chem. Soc. Rev.* **2012**, *41*, 448.
(16) Dale, J. A.; Dull, D. L.; Mosher, H. S. *Journal of Organic Chemistry* **1969**, *34*, 2543.
(17) Trost, B. M.; Bunt, R. C.; Pulley, S. R. *Journal of Organic Chemistry* **1994**, *59*, 4202.
(18) Tachibana, K.; Ohnishi, A. *J. Chromatogr. A* **2001**, *906*, 127.
(19) Stephens, P. J.; Devlin, F. J.; Pan, J. J. *Chirality* **2008**, *20*, 643.
(20) Parker, D. *Chemical Reviews* **1991**, *91*, 1441.
(21) Wenzel, T. J.; Wilcox, J. D. *Chirality* **2003**, *15*, 256.
(22) Pirkle, W. H. *Journal of the American Chemical Society* **1966**, *88*, 1837.
(23) Lovely, A. E.; Wenzel, T. J. *Organic Letters* **2006**, *8*, 2823.
(24) Lovely, A. E.; Wenzel, T. J. *Journal of Organic Chemistry* **2006**, *71*, 9178.
(25) Lovely, A. E.; Wenzel, T. J. *Tetrahedron-Asymmetry* **2006**, *17*, 2642.
(26) Perez-Trujillo, M.; Virgili, A. *Tetrahedron-Asymmetry* **2006**, *17*, 2842.
(27) Ardej-Jakubisiak, M.; Kawecki, R. *Tetrahedron-Asymmetry* **2008**, *19*, 2645.
(28) Moon, L. S.; Jolly, R. S.; Kasetti, Y.; Bharatam, P. V. *Chemical Communications* **2009**, 1067.
(29) Moon, L. S.; Pal, M.; Kasetti, Y.; Bharatam, P. V.; Jolly, R. S. *Journal of Organic Chemistry* **2010**, *75*, 5487.
(30) Bozkurt, S.; Durmaz, M.; Naziroglu, H. N.; Yilmaz, M.; Sirit, A. *Tetrahedron-Asymmetry* **2011**, *22*, 541.
(31) Guo, S.; Wang, G.; Ai, L. *Tetrahedron-Asymmetry* **2013**, *24*, 480.
(32) Mishra, S. K.; Chaudhari, S. R.; Suryaprakash, N. *Organic & Biomolecular Chemistry* **2014**, *12*, 495.

(33) Klika, K. D.; Mishra, S. K.; Chaudhari, S. R.; Suryaprakash, N. *Tetrahedron-Asymmetry* **2014**, *25*, 705.
(34) Yuste, F.; Sanchez-Obregon, R.; Diaz, E.; Garcia-Carrillo, M. A. *Tetrahedron-Asymmetry* **2014**, *25*, 224.
(35) Raban, M.; Mislow, K. *Tetrahedron Letters* **1965**, 4249.
(36) Dale, J. A.; Mosher, H. S. *Journal of the American Chemical Society* **1968**, *90*, 3732.
(37) Seco, J. M.; Latypov, S.; Quinoa, E.; Riguera, R. *Tetrahedron-Asymmetry* **1995**, *6*, 107.
(38) Latypov, S. K.; Seco, J. M.; Quinoa, E.; Riguera, R. *Journal of Organic Chemistry* **1995**, *60*, 1538.
(39) Seco, J. M.; Quinoa, E.; Riguera, R. *Chemical Reviews* **2004**, *104*, 17.
(40) Seco, J. M.; Latypov, S. K.; Quinoa, E.; Riguera, R. *Journal of Organic Chemistry* **1997**, *62*, 7569.
(41) Hoye, T. R.; Renner, M. K. *Journal of Organic Chemistry* **1996**, *61*, 8489.
(42) Hoye, T. R.; Renner, M. K. *Journal of Organic Chemistry* **1996**, *61*, 2056.
(43) Leiro, V.; Seco, J. M.; Quinoa, E.; Riguera, R. *Organic Letters* **2008**, *10*, 2729.
(44) Leiro, V.; Seco, J. M.; Quinoa, E.; Riguera, R. *Organic Letters* **2008**, *10*, 2733.
(45) Leiro, V.; Manuel Seco, J.; Quinoa, E.; Riguera, R. *Chemistry-an Asian Journal* **2010**, *5*, 2106.
(46) Seco, J. M.; Quinoa, E.; Riguera, R. *Journal of Organic Chemistry* **1999**, *64*, 4669.
(47) Dufrasne, F.; Gelbcke, M.; Neve, J. *Spectroc. Acta Pt. A-Molec. Biomolec. Spectr.* **2003**, *59*, 1239.
(48) Dufrasne, F.; Gelbcke, M.; Galanski, M. *Spectroc. Acta Pt. A-Molec. Biomolec. Spectr.* **2006**, *65*, 869.
(49) Chi, Y.; Peelen, T. J.; Gellman, S. H. *Organic Letters* **2005**, *7*, 3469.
(50) Chauvin, A.-S.; Bernardinelli, G.; Alexakis, A. *Tetrahedron-Asymmetry* **2006**, *17*, 2203.
(51) Mastranzo, V. M.; Quintero, L.; De Parrodi, C. A. *Chirality* **2007**, *19*, 503.
(52) Garner, A. C.; Hodgkinson, R. C.; Wallis, J. D. *Tetrahedron Letters* **2013**, *54*, 5583.
(53) Chin, J.; Kim, D. C.; Kim, H. J.; Panosyan, F. B.; Kim, K. M. *Organic Letters* **2004**, *6*, 2591.
(54) Sabot, C.; Mosser, M.; Antheaume, C.; Mioskowski, C.; Baati, R.; Wagner, A. *Chemical Communications* **2009**, 3410.
(55) Orlov, N. V.; Ananikov, V. P. *Chemical Communications* **2010**, *46*, 3212.
(56) Schurig, V. *J. Chromatogr. A* **2001**, *906*, 275.
(57) He, L. F.; Beesley, T. E. *J. Liq. Chromatogr. Relat. Technol.* **2005**, *28*, 1075.
(58) Schurig, V.; Nowotny, H. P. *Angew. Chem.-Int. Edit. Engl.* **1990**, *29*, 939.
(59) Zhang, Y.; Wu, D. R.; Wang-Iverson, D. B.; Tymiak, A. A. *Drug Discov. Today* **2005**, *10*, 571.
(60) Frank, H.; Nicholson, G. J.; Bayer, E. *J. Chromatogr. Sci.* **1977**, *15*, 174.
(61) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angewandte Chemie-International Edition* **1999**, *38*, 2398.
(62) Reetz, M. T.; Kuhling, K. M.; Wilensek, S.; Husmann, H.; Hausig, U. W.; Hermes, M. *Catal. Today* **2001**, *67*, 389.

(63) Leung, D.; Anslyn, E. V. *Journal of the American Chemical Society* **2008**, *130*, 12328.
(64) Olsen, B. A.; Wirth, D. D.; Larew, J. S. *J. Pharm. Biomed. Anal.* **1998**, *17*, 623.
(65) Tornoe, C. W.; Sonke, T.; Maes, I.; Schoemaker, H. E.; Meldal, M. *Tetrahedron-Asymmetry* **2000**, *11*, 1239.
(66) Sajonz, P.; Schafer, W.; Gong, X. Y.; Shultz, S.; Rosner, T.; Welch, C. J. *J. Chromatogr. A* **2007**, *1145*, 149.
(67) Hattori, T.; Minato, Y.; Yao, S. L.; Finn, M. G.; Miyano, S. *Tetrahedron Letters* **2001**, *42*, 8015.
(68) Joyce, L. A.; Maynor, M. S.; Dragna, J. M.; da Cruz, G. M.; Lynch, V. M.; Canary, J. W.; Anslyn, E. V. *Journal of the American Chemical Society* **2011**, *133*, 13746.
(69) You, L.; Pescitelli, G.; Anslyn, E. V.; Di Bari, L. *Journal of the American Chemical Society* **2012**, *134*, 7117.
(70) Bentley, K. W.; Nam, Y. G.; Murphy, J. M.; Wolf, C. *Journal of the American Chemical Society* **2013**, *135*, 18052.
(71) Nieto, S.; Dragna, J. M.; Anslyn, E. V. *Chemistry-a European Journal* **2010**, *16*, 227.
(72) Dragna, J. M.; Pescitelli, G.; Tran, L.; Lynch, V. M.; Anslyn, E. V.; Di Bari, L. *Journal of the American Chemical Society* **2012**, *134*, 4398.
(73) Leung, D.; Anslyn, E. V. *Organic Letters* **2011**, *13*, 2298.
(74) Barman, S.; Anslyn, E. V. *Tetrahedron* **2014**, *70*, 1357.
(75) Mei, X. F.; Wolf, C. *Journal of the American Chemical Society* **2006**, *128*, 13326.
(76) Bailey, D. M.; Hennig, A.; Uzunova, V. D.; Nau, W. M. *Chemistry-a European Journal* **2008**, *14*, 6069.
(77) Yu, S. S.; Plunkett, W.; Kim, M.; Pu, L. *Journal of the American Chemical Society* **2012**, *134*, 20282.
(78) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567.
(79) Hopfl, H. *J. Organomet. Chem.* **1999**, *581*, 129.
(80) Hamilton, C. W.; Baker, R. T.; Staubitz, A.; Manners, I. *Chem. Soc. Rev.* **2009**, *38*, 279.
(81) Frankland, E. *Justus Liebigs Ann. Chem.* **1862**, *124*, 129.
(82) Hattori, K.; Miyata, M.; Yamamoto, H. *Journal of the American Chemical Society* **1993**, *115*, 1151.
(83) Hattori, K.; Yamamoto, H. *Journal of Organic Chemistry* **1992**, *57*, 3264.
(84) Hattori, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749.
(85) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *Journal of the American Chemical Society* **1994**, *116*, 10520.
(86) Vargas, G.; Farfan, N.; Santillan, R.; Gutierrez, A.; Gomez, E.; Barba, V. *Inorganica Chimica Acta* **2005**, *358*, 2996.
(87) Barba, V.; Vazquez, J.; Lopez, F.; Santillan, R.; Farfan, N. *J. Organomet. Chem.* **2005**, *690*, 2351.
(88) Rodriguez, M.; Ochoa, M. E.; Santillan, R.; Farfan, N.; Barba, V. *J. Organomet. Chem.* **2005**, *690*, 2975.
(89) Barba, V.; Santillan, R.; Farfan, N. *Journal of the Brazilian Chemical Society* **2005**, *16*, 449.
(90) Barba, V.; Vargas, G.; Gomez, E.; Farfan, N. *Inorganica Chimica Acta* **2000**, *311*, 133.

(91) Wiskur, S. L.; Lavigne, J. J.; Ait-Haddou, H.; Lynch, V.; Chiu, Y. H.; Canary, J. W.; Anslyn, E. V. *Organic Letters* **2001**, *3*, 1311.
(92) James, T. D.; Sandanayake, K.; Shinkai, S. *J. Chem. Soc.-Chem. Commun.* **1994**, 477.
(93) Perez-Fuertes, Y.; Kelly, A. M.; Johnson, A. L.; Arimori, S.; Bull, S. D.; James, T. D. *Organic Letters* **2006**, *8*, 609.
(94) Perez-Fuertes, Y.; Kelly, A. M.; Fossey, J. S.; Powell, M. E.; Bull, S. D.; James, T. D. *Nature Protocols* **2008**, *3*, 210.
(95) Kelly, A. M.; Perez-Fuertes, Y.; Arimori, S.; Bull, S. D.; James, T. D. *Organic Letters* **2006**, *8*, 1971.
(96) Kelly, A. M.; Perez-Fuertes, Y.; Fossey, J. S.; Yeste, S. L.; Bull, S. D.; James, T. D. *Nature Protocols* **2008**, *3*, 215.
(97) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *Journal of Organic Chemistry* **1973**, *38*, 2143.
(98) Chopard, C.; Azerad, R.; Prange, T. *J. Mol. Catal. B-Enzym.* **2008**, *50*, 53.
(99) Shabbir, S. H.; Regan, C. J.; Anslyn, E. V. *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106*, 10487.
(100) Shabbir, S. H.; Joyce, L. A.; da Cruz, G. M.; Lynch, V. M.; Sorey, S.; Anslyn, E. V. *Journal of the American Chemical Society* **2009**, *131*, 13125.
(101) Urabe, D.; Todoroki, H.; Masuda, K.; Inoue, M. *Tetrahedron* **2012**, *68*, 3210.
(102) Li, Z.; Chen, C.; Groeger, S.; Kressler, J. *Polymer* **2012**, *53*, 2613.
(103) Fordred, P. S.; Bull, S. D. *Tetrahedron Letters* **2013**, *54*, 27.
(104) Shi, C.; Geders, T. W.; Park, S. W.; Wilson, D. J.; Boshoff, H. I.; Abayomi, O.; Barry, C. E.; Schnappinger, D.; Finzel, B. C.; Aldrich, C. C. *Journal of the American Chemical Society* **2011**, *133*, 18194.
(105) Kelly, A. M.; Bull, S. D.; James, T. D. *Tetrahedron-Asymmetry* **2008**, *19*, 489.
(106) Powell, M. E.; Kelly, A. M.; Bull, S. D.; James, T. D. *Tetrahedron Letters* **2009**, *50*, 876.
(107) Yeste, S. L.; Powell, M. E.; Bull, S. D.; James, T. D. *Journal of Organic Chemistry* **2009**, *74*, 427.
(108) Mirri, G.; Bull, S. D.; Horton, P. N.; James, T. D.; Male, L.; Tucker, J. H. R. *Journal of the American Chemical Society* **2010**, *132*, 8903.
(109) Metola, P.; Anslyn, E. V.; James, T. D.; Bull, S. D. *Chem. Sci.* **2012**, *3*, 156.
(110) Chaudhari, S. R.; Suryaprakash, N. R. *New Journal of Chemistry* **2014**, *38*, 790.
(111) Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27.
(112) Gawronski, J.; Wascinska, N.; Gajewy, J. *Chemical Reviews* **2008**, *108*, 5227.
(113) Byrne, J. J.; Chavarot, M.; Chavant, P. Y.; Vallee, Y. *Tetrahedron Letters* **2000**, *41*, 873.
(114) Huang, J. K.; Corey, E. J. *Organic Letters* **2004**, *6*, 5027.
(115) Merino, P.; Marques-Lopez, E.; Tejero, T.; Herrera, R. P. *Tetrahedron* **2009**, *65*, 1219.
(116) Harada, K. *Nature* **1963**, *200*, 1201.
(117) Stout, D. M.; Black, L. A.; Matier, W. L. *Journal of Organic Chemistry* **1983**, *48*, 5369.
(118) Tulinsky, J.; Cheney, B. V.; Mizsak, S. A.; Watt, W.; Han, F.; Dolak, L. A.; Judge, T.; Gammill, R. B. *Journal of Organic Chemistry* **1999**, *64*, 93.

(119) Yamabe, S.; Zeng, G. X.; Guan, W.; Sakaki, S. *Beilstein J. Org. Chem.* **2014**, *10*, 1765.
(120) Gudmundsson, K. S.; Boggs, S. D.; Catalano, J. G.; Svolto, A.; Spaltenstein, A.; Thomson, M.; Wheelan, P.; Jenkinson, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6399.
(121) Zhong, H. M.; Cohen, J. H.; Abdel-Magid, A. F.; Kenney, B. D.; Maryanoff, C. A.; Shah, R. D.; Villani, F. J.; Zhang, F.; Zhang, X. N. *Tetrahedron Letters* **1999**, *40*, 7721.
(122) Cohen, J. H.; Abdel-Magid, A. F.; Almond, H. R.; Maryanoff, C. A. *Tetrahedron Letters* **2002**, *43*, 1977.
(123) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.
(124) Nieto, S.; Arnau, P.; Serrano, E.; Navarro, R.; Soler, T.; Cativiela, C.; Urriolabeitia, E. P. *Inorg. Chem.* **2009**, *48*, 11963.
(125) Hogg, J. H.; Ollmann, I. R.; Haeggstrom, J. Z.; Wetterholm, A.; Samuelsson, B.; Wong, C. H. *Bioorganic & Medicinal Chemistry* **1995**, *3*, 1405.
(126) Hanna, P. E. *Current Medicinal Chemistry* **1996**, *3*, 195.
(127) Igarashi, N.; Moriyama, H.; Fujiwara, T.; Fukumori, Y.; Tanaka, N. *Nature Structural Biology* **1997**, *4*, 276.
(128) Vigh, L.; Literati, P. N.; Horvath, I.; Torok, Z.; Balogh, G.; Glatz, A.; Kovacs, E.; Boros, I.; Ferdinandy, P.; Farkas, B.; Jaszlits, L.; Jednakovits, A.; Koranyi, L.; Maresca, B. *Nature Medicine* **1997**, *3*, 1150.
(129) Bode, J. W.; Fox, R. M.; Baucom, K. D. *Angewandte Chemie-International Edition* **2006**, *45*, 1248.
(130) Pusterla, I.; Bode, J. W. *Angewandte Chemie-International Edition* **2012**, *51*, 513.
(131) Smithen, D. A.; Mathews, C. J.; Tomkinson, N. C. O. *Organic & Biomolecular Chemistry* **2012**, *10*, 3756.
(132) Chernega, A. N.; Davies, S. G.; Goodwin, C. J.; Hepworth, D.; Kurosawa, W.; Roberts, P. M.; Thomson, J. E. *Organic Letters* **2009**, *11*, 3254.
(133) Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron* **1985**, *41*, 3455.
(134) Chang, Z. Y.; Coates, R. M. *Journal of Organic Chemistry* **1990**, *55*, 3464.
(135) Jost, S.; Gimbert, Y.; Greene, A. E.; Fotiadu, F. *Journal of Organic Chemistry* **1997**, *62*, 6672.
(136) Fassler, R.; Frantz, D. E.; Oetiker, J.; Carreira, E. M. *Angewandte Chemie-International Edition* **2002**, *41*, 3054.
(137) Goti, A.; Cicchi, S.; Mannucci, V.; Cardona, F.; Guarna, F.; Merino, P.; Tejero, T. *Organic Letters* **2003**, *5*, 4235.
(138) Nguyen, T. B.; Martel, A.; Dhal, R.; Dujardin, G. *Organic Letters* **2008**, *10*, 4493.
(139) Hoshino, Y.; Yamamoto, H. *Journal of the American Chemical Society* **2000**, *122*, 10452.
(140) Zhang, W.; Yamamoto, H. *Journal of the American Chemical Society* **2007**, *129*, 286.
(141) Hanselmann, R.; Zhou, J. C.; Ma, P.; Confalone, P. N. *Journal of Organic Chemistry* **2003**, *68*, 8739.
(142) Bentley, S. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Toms, S. M. *Tetrahedron* **2010**, *66*, 4604.
(143) Wang, L.; Phanstiel, O. *Journal of Organic Chemistry* **2000**, *65*, 1442.
(144) Snider, B. B.; Lin, H. *Journal of the American Chemical Society* **1999**, *121*, 7778.

(145) Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B.; Adams, J. P. *Journal of the American Chemical Society* **1999**, *121*, 4900.
(146) Patel, S. K.; Murat, K.; Py, S.; Vallee, Y. *Organic Letters* **2003**, *5*, 4081.
(147) White, J. D.; Hansen, J. D. *Journal of Organic Chemistry* **2005**, *70*, 1963.
(148) Wittman, M. D.; Halcomb, R. L.; Danishefsky, S. J. *Journal of Organic Chemistry* **1990**, *55*, 1981.
(149) Wang, Q. X. H.; King, J.; Phanstiel, O. *Journal of Organic Chemistry* **1997**, *62*, 8104.
(150) Tokuyama, H.; Kuboyama, T.; Amano, A.; Yamashita, T.; Fukuyama, T. *Synthesis-Stuttgart* **2000**, 1299.
(151) Heydari, A.; Aslanzadeh, S. *Advanced Synthesis & Catalysis* **2005**, *347*, 1223.
(152) Patel, I.; Smith, N. A.; Tyler, S. N. G. *Organic Process Research & Development* **2009**, *13*, 49.
(153) Feuer, H.; Vincent, B. F. *Journal of the American Chemical Society* **1962**, *84*, 3771.
(154) Oppolzer, W.; Tamura, O. *Tetrahedron Letters* **1990**, *31*, 991.
(155) Clayden, J.; Greeves, N.; Warren, S.; 2 ed.; Oxford: 2012, p 229.
(156) Belzecki, C.; Panfil, I. *Journal of Organic Chemistry* **1979**, *44*, 1212.
(157) Grundke, G.; Keese, W.; Rimpler, M. *Synthesis-Stuttgart* **1987**, 1115.
(158) Kliegel, W.; Nanninga, D. *J. Organomet. Chem.* **1983**, *247*, 247.
(159) Groziak, M. P.; Chen, L. Y.; Yi, L.; Robinson, P. D. *Journal of the American Chemical Society* **1997**, *119*, 7817.
(160) Dewar, M. J. S.; Dougherty, R. C. *Journal of the American Chemical Society* **1962**, *84*, 2648.
(161) Dewar, M. J. S.; Dougherty, R. C. *Journal of the American Chemical Society* **1964**, *86*, 433.
(162) Dewar, M. J. S.; Jones, R. *Journal of the American Chemical Society* **1967**, *89*, 2408.
(163) Davis, F. A.; Dewar, M. J. S.; Jones, R. *Journal of the American Chemical Society* **1968**, *90*, 706.
(164) Snyder, H. R.; Reedy, A. J.; Lennarz, W. J. *Journal of the American Chemical Society* **1958**, *80*, 835.
(165) Haynes, R. R.; Snyder, H. R. *Journal of Organic Chemistry* **1964**, *29*, 3229.
(166) Tschampel, P.; Snyder, H. R. *Journal of Organic Chemistry* **1964**, *29*, 2168.
(167) Dunn, H. E.; Catlin, J. C.; Snyder, H. R. *Journal of Organic Chemistry* **1968**, *33*, 4483.
(168) Catlin, J. C.; Snyder, H. R. *Journal of Organic Chemistry* **1969**, *34*, 1660.
(169) Kolodiazhnyi, O. I.; Demchuk, O. M.; Gerschkovich, A. A. *Tetrahedron-Asymmetry* **1999**, *10*, 1729.
(170) Caselli, E.; Danieli, C.; Morandi, S.; Bonfiglio, B.; Forni, A.; Prati, F. *Organic Letters* **2003**, *5*, 4863.
(171) Tickell, D. A.; Mahon, M. F.; Bull, S. D.; James, T. D. *Organic Letters* **2013**, *15*, 860.
(172) Horeau, A. *Tetrahedron Letters* **1969**, 3121.
(173) Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973**, *29*, 1055.
(174) Horeau, A.; Guette, J. P. *Tetrahedron* **1974**, *30*, 1923.
(175) Satyanarayana, T.; Kagan, H. B. *Chemistry-a European Journal* **2006**, *12*, 5785.

(176) Girard, C.; Kagan, H. B. *Angewandte Chemie-International Edition* **1998**, *37*, 2923.
(177) Kagan, H. B. *Synlett* **2001**, 888.
(178) Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *Journal of the American Chemical Society* **1986**, *108*, 2353.
(179) Pasquier, M. L.; Marty, W. *Angew. Chem.-Int. Edit. Engl.* **1985**, *24*, 315.
(180) Feringa, B. L.; Smaardijk, A.; Wynberg, H. *Journal of the American Chemical Society* **1985**, *107*, 4798.
(181) Feringa, B. L.; Smaardijk, A. A.; Wynberg, H.; Strijtveen, B.; Kellogg, R. M. *Tetrahedron Letters* **1986**, *27*, 997.
(182) Strijtveen, B.; Feringa, B. L.; Kellogg, R. M. *Tetrahedron* **1987**, *43*, 123.
(183) Feringa, B. L.; Strijtveen, B.; Kellogg, R. M. *Journal of Organic Chemistry* **1986**, *51*, 5484.
(184) Marinetti, A.; Mathey, F.; Ricard, L. *Organometallics* **1993**, *12*, 1207.
(185) Grotjahn, D. B.; Joubran, C. *Tetrahedron-Asymmetry* **1995**, *6*, 745.
(186) Heumann, A.; Loutfi, A.; Ortiz, B. *Tetrahedron-Asymmetry* **1995**, *6*, 1073.
(187) Alvarez, C.; Barkaoui, L.; Goasdoue, N.; Daran, J. C.; Platzer, N.; Rudler, H.; Vaissermann, J. *J. Chem. Soc.-Chem. Commun.* **1989**, 1507.
(188) Coulbeck, E.; Eames, J. *Tetrahedron-Asymmetry* **2009**, *20*, 635.
(189) Fleming, I.; Ghosh, S. K. *J. Chem. Soc.-Chem. Commun.* **1994**, 99.
(190) Fleming, I.; Ghosh, S. K. *J. Chem. Soc.-Perkin Trans. 1* **1998**, 2733.
(191) Suginome, M.; Iwanami, T.; Ohmori, Y.; Matsumoto, A.; Ito, Y. *Chemistry-a European Journal* **2005**, *11*, 2954.
(192) Grassi, M.; Disilvestro, G.; Farina, M. *Tetrahedron* **1985**, *41*, 177.
(193) Darrigo, P.; Feliciotti, L.; PedrocchiFantoni, G.; Servi, S. *Journal of Organic Chemistry* **1997**, *62*, 6394.
(194) Khiar, N.; Salvador, A.; Valdivia, V.; Chelouan, A.; Alcudia, A.; Alvarez, E.; Fernandez, I. *Journal of Organic Chemistry* **2013**, *78*, 6510.
(195) Hoffmann, R. W.; Schopfer, U.; Muller, C.; Brandl, T. *Helvetica Chimica Acta* **2002**, *85*, 4424.
(196) Satyanarayana, T.; Kagan, H. B. *Tetrahedron* **2007**, *63*, 6415.
(197) Periasamy, M.; Venkatraman, L.; Thomas, K. R. J. *Journal of Organic Chemistry* **1997**, *62*, 4302.
(198) Kaufmann, D.; Boese, R. *Angew. Chem.-Int. Edit. Engl.* **1990**, *29*, 545.
(199) Paine, J. B. *Journal of Organic Chemistry* **2008**, *73*, 4939.
(200) Blackmond, D. G. *Cold Spring Harbor Perspect. Biol.* **2010**, *2*.
(201) Soai, K.; Shibata, T.; Sato, I. *Accounts Chem. Res.* **2000**, *33*, 382.
(202) Ruiz-Mirazo, K.; Briones, C.; de la Escosura, A. *Chemical Reviews* **2014**, *114*, 285.
(203) Soai, K.; Shibata, T.; Morioka, H.; Choji, K. *Nature* **1995**, *378*, 767.
(204) Blackmond, D. G.; McMillan, C. R.; Ramdeehul, S.; Schorm, A.; Brown, J. M. *Journal of the American Chemical Society* **2001**, *123*, 10103.
(205) Blackmond, D. G. *Tetrahedron-Asymmetry* **2006**, *17*, 584.
(206) Gehring, T.; Quaranta, M.; Odell, B.; Blackmond, D. G.; Brown, J. M. *Angewandte Chemie-International Edition* **2012**, *51*, 9539.
(207) Klussmann, M.; Izumi, T.; White, A. J. P.; Armstrong, A.; Blackmond, D. G. *Journal of the American Chemical Society* **2007**, *129*, 7657.
(208) Klussmann, M.; Iwamura, H.; Mathew, S. P.; Wells, D. H.; Pandya, U.; Armstrong, A.; Blackmond, D. G. *Nature* **2006**, *441*, 621.

(209) Klussmann, M.; Mathew, S. R.; Iwamura, H.; Wells, D. H.; Armstrong, A.; Blackmond, D. G. *Angewandte Chemie-International Edition* **2006**, *45*, 7989.
(210) Carman, R. M.; Klika, K. D. *Aust. J. Chem.* **1991**, *44*, 895.
(211) Diter, P.; Taudien, S.; Samuel, O.; Kagan, H. B. *Journal of Organic Chemistry* **1994**, *59*, 370.
(212) Rebière, F.; Riant, O.; Ricard, L.; Kagan, H. B. *Angewandte Chemie International Edition in English* **1993**, *32*, 568.
(213) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D. Q.; Zhang, X. L. *Journal of Organic Chemistry* **1992**, *57*, 2768.
(214) Kitahara, K.; Toma, T.; Shimokawa, J.; Fukuyama, T. *Organic Letters* **2008**, *10*, 2259.
(215) Marshall, P. A.; Prager, R. H. *Aust. J. Chem.* **1977**, *30*, 141.
(216) Russell, G. A.; Mikol, G. J. *Journal of the American Chemical Society* **1966**, *88*, 5498.